Draft Comparative Effectiveness Review

Number XX

Interventions to Improve Appropriate Antibiotic Use for Acute Respiratory Tract Infections

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the review questions and methodology at the outset of this report, the EPC with consulted several technical and content experts, reflecting a variety of viewpoints relevant to this topic. It is expected that technical experts consulted will have divergent and possibly conflicted opinions, and that this diversity is helpful in achieving a well-rounded report. The study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report will be added for the final version.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers who participated in reviewing this report will be added for the final version.

Interventions to Improve Appropriate Antibiotic Use for Acute Respiratory Tract Infections

Structured Abstract

Objectives. To assess the comparative effectiveness interventions for reducing antibiotic use when not indicated for acute respiratory tract infections (RTIs) in adults and children.

Data Sources. Electronic databases **(**Ovid MEDLINE® from 1990 and the Cochrane Library from 2005 to March 2014), reference lists of included systematic reviews, and Scientific Information Packets submitted by manufacturers of point-of-care tests and experts.

Review Methods. Using predefined criteria, we selected studies of any intervention with a stated goal of improving appropriate prescribing of antibiotics for any patients with acute RTIs. Key outcomes were appropriate prescribing and resistance. Also included were undesirable consequences, such as medical complications and satisfaction, and knowledge and time burden. We prioritized randomized controlled trials (RCTs) and cohort studies with concurrent controls, but also considered historically-controlled or uncontrolled studies with adequate adjustment for confounders. The quality of included studies was rated, data were extracted, and the strength of the evidence for key outcomes was assessed. Results were mainly qualitatively synthesized.

Results. Of 6,021 citations identified in searches, a total of 87 trials, 39 observational studies, and 3 systematic reviews were included. Important limitations of the evidence include that the most important benefits and harms were under reported and that only 45 percent of the studies were conducted in the United States. Four intervention types stood out as having the best evidence of benefit over usual care because they improved resistance or appropriate prescribing: **(1) Watchful waiting** was the only intervention that had any evidence of reducing **resistance** to 4-6 antibiotics compared with immediate prescribing (28% vs 56%; $P<0.02$); however, it was low strength (1 RCT, N=223) and limited to children with acute otitis media. Various other types of delayed prescribing approaches also resulted in lower rates of antibiotic use compared with immediate prescribing (absolute difference, range, -63% to -76%; 6 RCTs; N=1664), without any important consequences; **(2) Electronic Decision Support** had moderate strength evidence of reducing **inappropriate** prescribing in acute bronchitis and acute otitis media (range, -13% to -24%; 2 RCTs, N=12195), with low-strength evidence of no worsening of healthcare utilization or complications; **(3) Two combined clinic-based education interventions** that targeted patients, parents, and clinicians had low strength evidence of reducing **inappropriate** prescribing in children with pharyngitis and in adults with sinusitis (-10% to -27%; 1 RCT, 1 observational, N=2193); and **(4) A multifaceted intervention that combined a clinical algorithm, clinical tutor training, and provider education** had low strength evidence of improving **appropriate** prescribing in patients with acute RTI in Mexico (+21.5%; 1 observational; N=1495), but its net benefit was unknown because potential consequences were note evaluated. The next tier of best evidence is for interventions with the highest reductions in overall prescriptions with no important consequences. For this next tier, procalcitonin stood out with the strongest evidence of reducing overall antibiotic prescribing for adults (absolute difference range, -12% to -72%; moderate strength; 5 RCTs; N=2820), with no impact on mortality. Head-to-head studies primarily focused on clinical interventions and the main

difference was that the FeverPain clinical score led to fewer overall antibiotic prescriptions for sore throat than delayed prescribing (-9%) and a 1 day reduction of moderate symptoms (low strength; 1 RCT, N=631).

Conclusions. A large body of evidence is largely inadequate to identify optimum intervention strategies for improving appropriate antibiotic use for acute RTIs because of outcome reporting gaps. The four intervention types that stood out as having the best evidence of overall effectiveness were: (1) delayed prescribing; (2) Electronic decision support; (3) clinic-based education programs that target patients, parents, and clinicians; and (4) a multi-faceted intervention that combined a clinical algorithm, clinical tutor training, and provider education. Future studies with rigorous designs should assess appropriate prescribing and resistance to antibiotics and evaluate the impact of important potential effect modifiers.

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Executive Summary

Introduction

Antibiotics transformed the practice of medicine in the last half of the 20th century. With antibiotics, common infections and injuries that would previously have caused death or debility could now be effectively treated and cured. Due to their exquisite adaptability, however, bacteria have a great capacity to develop resistance to antibiotics and the problem of resistant strains of bacteria has grown substantially. In the United States each year, at least 2 million people acquire infections with antibiotic resistant bacteria and 23,000 people die of such infections.[1] For decades, there has been increasing awareness that using antibiotics to treat nonbacterial and/or benign self-limiting illnesses contributes to the development of antibiotic-resistant bacteria[2-4] and may be the most important factor in the development of antibiotic resistance.[1] Improving appropriate antibiotic use is, therefore, critical to arresting the growing prevalence of antibiotic-resistant bacteria.[5] In addition to being the chief factor in the development of antibiotic resistance, inappropriate use of antibiotics unnecessarily exposes patients to potential adverse side effects and increases medical costs.

The problem of inappropriate antibiotic use may be biggest for acute respiratory tract infections (RTIs). Acute RTIs include acute bronchitis, otitis media, pharyngitis/tonsillitis, rhinitis, sinusitis, and other viral syndromes.[6] Despite guidelines recommending no antibiotic treatment for most acute RTIs, the majority of outpatient antibiotic prescriptions in the United States are for acute RTIs. In 1998, an estimated 76 million ambulatory office visits for acute RTIs resulted in 41 million antibiotic prescriptions.[7] A 2013 report regarding healthy adults visiting outpatient offices and emergency departments (EDs) for acute bronchitis revealed prescriptions for antibiotics were given at 73 percent of visits between 1996 and 2010,[8] despite the fact that the majority of acute bronchitis cases are caused by viral pathogens for which antibiotics are not helpful.

The reasons for inappropriate use of antibiotics for acute RTIs are numerous, diverse, complex, and not well understood. Consequently, strategies to improve appropriate use of antibiotics for RTIs have varied in whose behavior they are designed to change, for example, clinicians, patients, parents, healthy individuals in the general population, or policymakers. Intervention strategies have also varied in the means by which they are designed to change antibiotic prescribing behavior, including education; strategies to improve communication between clinicians and patients; clinical strategies, such as delayed prescribing or use of point-of-care diagnostic tests; system level strategies, such as clinician reminders or audit and feedback; or multifaceted approaches that incorporate various elements.

In evaluating interventions to improve appropriate prescribing and use of antibiotics, the most direct outcomes of interest are antibiotic resistance and changes in appropriate prescribing and use. There is no consensus on how to measure appropriate prescribing as an outcome. Given that studies find that half or more of overall antibiotic prescriptions for various RTIs are not necessary,[5,9,10] measures of overall change in antibiotic prescription or use are a relevant, albeit limited, proxy for changes in appropriate use. The usefulness of overall prescribing as a proxy for appropriate prescribing may vary based on background factors and we do not know precisely how good of a proxy measure it is because the estimates of the rate of overall prescribing that is inappropriate/appropriate range so widely, from 50 to 80 percent. Interventions to improve appropriate antibiotic use may also have a variety of potentially undesirable outcomes that are important to measure. For example, if efforts to improve appropriate antibiotic use resulted in

under-treatment of patients for whom antibiotics would have been indicated, undesirable outcomes such as medical complications, hospital admissions, and mortality might increase. Similarly, reduced prescription of antibiotics may lead to increased clinic visits, longer duration of symptoms, or longer time to return to school or work. Depending on patients' expectations, patient satisfaction may also be affected. The interventions themselves also may require substantial time and resources. In addition, relevant intermediate outcomes include improved knowledge regarding the use of antibiotics for acute RTI and improved shared decisionmaking skills in patients and clinicians.

A report that ascertained the comparative effectiveness of various strategies, including the use of point-of-care testing, to improve the appropriate use of antibiotics for acute RTIs could be used broadly to inform clinical decisionmaking for patients, clinicians, and payers. While there have been prior systematic reviews of interventions to improve appropriate antibiotic prescribing for acute RTIs, their usefulness is limited by scope (assessing only one intervention or population), evidence base (older reviews, limited outcomes assessed), or lack of assessment of the *comparative* effectiveness of different strategies in different patients under different circumstances. These reviews leave gaps in knowledge about competing interventions, populations and outcomes.

Scope and Key Questions

The goal of the present systematic evidence review is to assess the comparative effectiveness of a breadth of possible strategies for improving appropriate antibiotic use for acute RTIs in adults and children. The Key Questions used to guide this report are shown below.

Key Question 1. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effectiveness of particular strategies in improving the appropriate prescription or use of antibiotics compared with other strategies or standard care?

Key Question 2. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on antibiotic resistance compared with other strategies or standard care?

Key Question 3. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on medical complications (including mortality, hospitalization and adverse effects of receiving or not receiving antibiotics) compared with other strategies or standard care?

Key Question 4. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on other clinical outcomes (e.g., health care utilization, patient satisfaction) compared with other strategies or standard care?

Key Question 5. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on achieving intended intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute respiratory tract infections (clinicians and/or patients), improved shared decision making

regarding the use of antibiotics, and improved clinician skills for appropriate antibiotic use (e.g., communication appropriate for patients' literacy level and/or cultural background)?

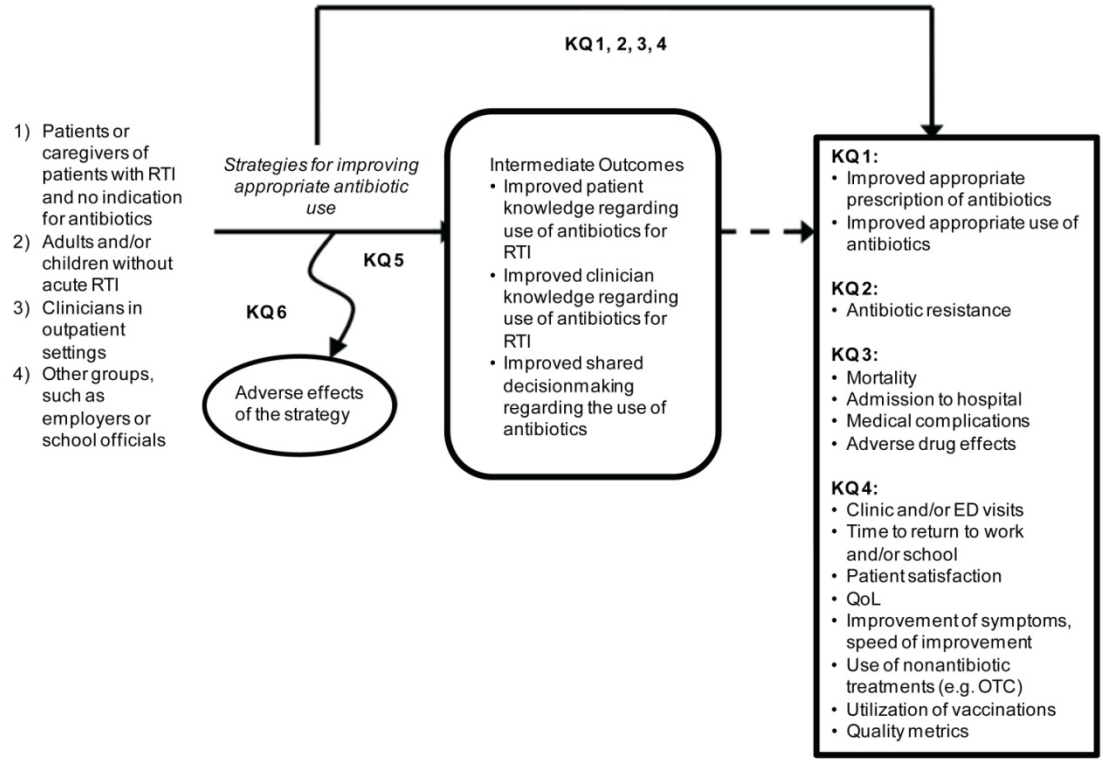
Key Question 6. What are the comparative nonclinical adverse effects of strategies for improving the appropriate use of antibiotics for acute respiratory tract infections (e.g., increased time burden on clinicians, patients, clinic staff)?

For Key Questions 1 through 4 the following subquestions were also addressed:

a) Does the comparative effectiveness of strategies differ according to how appropriateness is defined? (Key Question 1 only)
b) Does the comparative effectiveness of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
c) Does the comparative effectiveness of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
d) Does the comparative effectiveness of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
e) Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
f) Does the comparative effectiveness differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), system level characteristics, or whether the intervention was locally tailored?

The Key Questions are placed in relation to one another and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) in the analytic framework (Figure A). Specific details regarding patient population, intervention components, and outcomes are provided in the next section.

Figure A. Analytic framework for improving appropriate antibiotic use for acute respiratory tract infections



ED = emergency department, OTC = over-the-counter, QOL = quality of life, RTI = respiratory tract infection

Methods

This Comparative Effectiveness Review follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[11] All methods were determined a priori. The protocol is registered with the PROSPERO international database of prospectively registered systematic reviews.[12]

Literature Search Strategy

Our medical librarian searched Ovid MEDLINE® and Cochrane Central Register of Controlled Trials (CCRCT) from 1990 to May 14, 2014 and the Cochrane Database of Systematic Reviews (CDSR) from 2005 to March 2014. Additional sources searched included systematic review reference lists, Scientific Information Packets, consulting Technical Expert Panel (TEP) members.

Inclusion and Exclusion Criteria

Studies were included based on the PICOTS detailed below (Table A). Based on input from our TEP, and as we recognized that the 1990s mark the decade when many organizations, such as the Centers for Disease Control and Prevention, initiated formal efforts to promote appropriate antibiotic use, the Pacific Northwest Evidence-based Practice Center restricted inclusion to

studies published since 1990. Due to resource limitations, we only included studies published in English. Studies published in other languages but otherwise appearing to be eligible based on the title or English-language abstract were identified and reviewed in order to evaluate potential language bias.

Table A. Criteria for eligibility based 0n PICOTS framework

PICOTS	Criteria for Eligibility
Populations	Adult and pediatric patients with an acute RTI and no clear indication for antibiotic treatment. RTOs of interest include: acute bronchitis, AOM, sore throat/pharyngitis/tonsillitis, rhinitis, sinusitis, cough, and common cold.[6] Parents of pediatric patients with acute RTI and no clear indication for antibiotic treatment. Healthy adults and/or children without a current acute RTI, who may develop an acute RTI in the future. Clinicians and others who care for patients with acute RTI in outpatient settings. Groups whose attendance policies may indirectly affect the use of antibiotics, such as employers or school officials
Interventions	Any strategy for improving appropriate use of antibiotics when not indicated for acute RTI, which fall into various categories, including: Educational, behavioral and psychological interventions that target clinicians, patients, or both. Strategies to improve communication between clinicians and patients, such as those designed to improve shared decisionmaking. Clinical strategies such as delayed prescribing of antibiotics, clinical prediction rules, use of risk assessment or diagnostic prediction, use of nonantibiotic alternatives, or use of relevant point-of-care diagnostic tests. Any point-of-care test that is available and used in primary care settings for diagnostic purposes with the ability to provide results within a reasonable period of time (e.g. during the clinic visit). Examples include inflammatory tests (e.g., procalcitonin, CRP, white blood cell, etc.), rapid multiplex PCR tests used to rule in/out organisms (e.g. rapid strep test, influenza, RSV), and routine diagnostic tests, such as chest x-ray, pulse oximetry, and blood gasses, when they are specifically evaluated as an intervention for improving antibiotic use. System level strategies such as clinician reminders (paper-based or electronic), clinician audit and feedback, financial or regulatory incentives for clinicians or patients, antimicrobial stewardship programs, and pharmacist review. Multifaceted approaches that include numerous elements of one or more of the above strategies
Comparators	Different strategies for improving appropriate use of antibiotics when not indicated for acute RTI. Standard care without a strategy for improving appropriate use of antibiotics

PICOTS	Criteria for Eligibility
Outcomes	**Key Question 1** Increased appropriate prescription of antibiotics (primary outcome). Increased appropriate use of antibiotics (primary outcome). **Key Question 2** Antibiotic resistance. **Key Question 3** Mortality. Admission to hospital. Medical complications. Adverse drug effects, including *clostridium difficile* infections. **Key Question 4** Clinic visits (index, return and subsequent episodes), ED visits. Time to return to work and/or school. Patient satisfaction Quality of life. Improvement in patient symptoms, speed of improvement. Use of nonantibiotic treatments, such as over-the-counter medications. **Key Question 5** Intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute RTI (clinician and/or patient), or improved shared decisionmaking. **Key Question 6** Adverse effects of the strategy, such as increased time burden on clinicians, sustainability of intervention (e.g. measures of continued effectiveness over time), diagnostic resource use associated with point-of-care testing, diagnostic coding (e.g., ICD billing codes) according to desired action (prescribe/not prescribe).
Timing	Any duration of followup was eligible
Setting	Outpatient care settings including institutional settings, emergency care settings and other settings, such as school or workplace
Study Designs	Systematic Reviews with similar scope and search dates within past 3 years. RCTs Prospective and retrospective cohort studies including database studies For areas in which such direct comparative evidence is lacking, we included before-after studies that used methods to control for potential confounding and studies with a time-series design that evaluated temporal trends.

CRP = C-reactive protein; ED = emergency department; PCR = polymerase chain reaction; RCT = randomized controlled trial; RTI = respiratory tract infection

Study Selection

Study selection followed AHRQ guidance for reducing bias.[13,14] Abstracts for citations identified through searches were screened for eligibility by one reviewer, with any deemed ineligible reviewed by a second reviewer. Full-text of all citations deemed potentially eligible for inclusion by at least one reviewer were obtained for further evaluation by two reviewers, with differences in judgment on eligibility resolved through consensus or inclusion of a third party.

Data Extraction

Study characteristics and results were abstracted from included studies. One reviewer abstracted study data and a second reviewer appraised the abstractions. Intention-to-treat results were recorded if available. We considered potential effect modifiers or sources of heterogeneity, which are listed in Table B, below.

Table B. Potential sources of heterogeneity

Category	Sources of Heterogeneity
Populations	Type of RTI, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior RTIs, and prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained
Interventions	Clinician characteristics: Specialty, number of years in practice, type of clinic organization, geographic region, and population served Diagnostic method or definition used Clinician's perception of the patient's illness severity Clinician's diagnostic certainty Local tailoring Accuracy of diagnostic tests
Outcomes	Appropriate prescription/use: Definition of appropriateness Antibiotic resistance: Data source (i.e., population vs. study sample)
Setting	Time of year; during a disease epidemic or outbreak period

RTI = respiratory tract infection

Quality (Risk of Bias) Assessment of Individual Studies

The internal validity (quality) of systematic reviews, RCTs, and observational studies were assessed based on predefined criteria established by the Drug Effectiveness Review Project.[15] All assessments were done at the overall study level and resulted in a rating of good, fair, or poor. Studies that had a fatal flaw were rated poor in quality, studies that met all criteria were rated good in quality, and the remainder were rated fair in quality. We utilized a dual rating procedure for study quality, where all studies were first rated by one reviewer and then checked by another reviewer. All disagreements were resolved using a consensus process.

Data Synthesis

A hierarchy of evidence approach was used, where the best evidence is the focus of our synthesis for each question. We planned to synthesize outcome data quantitatively using meta-analysis to pool outcomes where appropriate. However, most data were not suitable for pooling due to heterogeneity of included studies. We synthesized the evidence qualitatively by grouping studies by similarity of population and/or intervention characteristics, including the sources of variation or heterogeneity listed above.

Strength of the Body of Evidence

We used methods outlined in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews to grade strength of evidence.[13,16] After consultation with the TEP members, we prioritized the following outcomes: appropriate antibiotic prescription, antibiotic resistance, medical complications, adverse drug effects, admission to hospital, clinic/ED visits, improvement in patient symptoms, quality of life, and adverse effects of the intervention. Domains considered in grading the strength of evidence included study limitations, consistency, directness, precision, and reporting bias with the body of evidence assigned a strength-of-evidence grade of high, moderate, or low. In cases where evidence did not exist, was sparse, or contained irreconcilable inconsistency, a grade of insufficient evidence was assigned.

Applicability

We assessed applicability by analyzing study eligibility criteria, characteristics of the enrolled population in comparison to the target population, characteristics of the interventions,

and comparators compared with care models currently in use, and clinical relevance and timing of the outcome measures.[17]

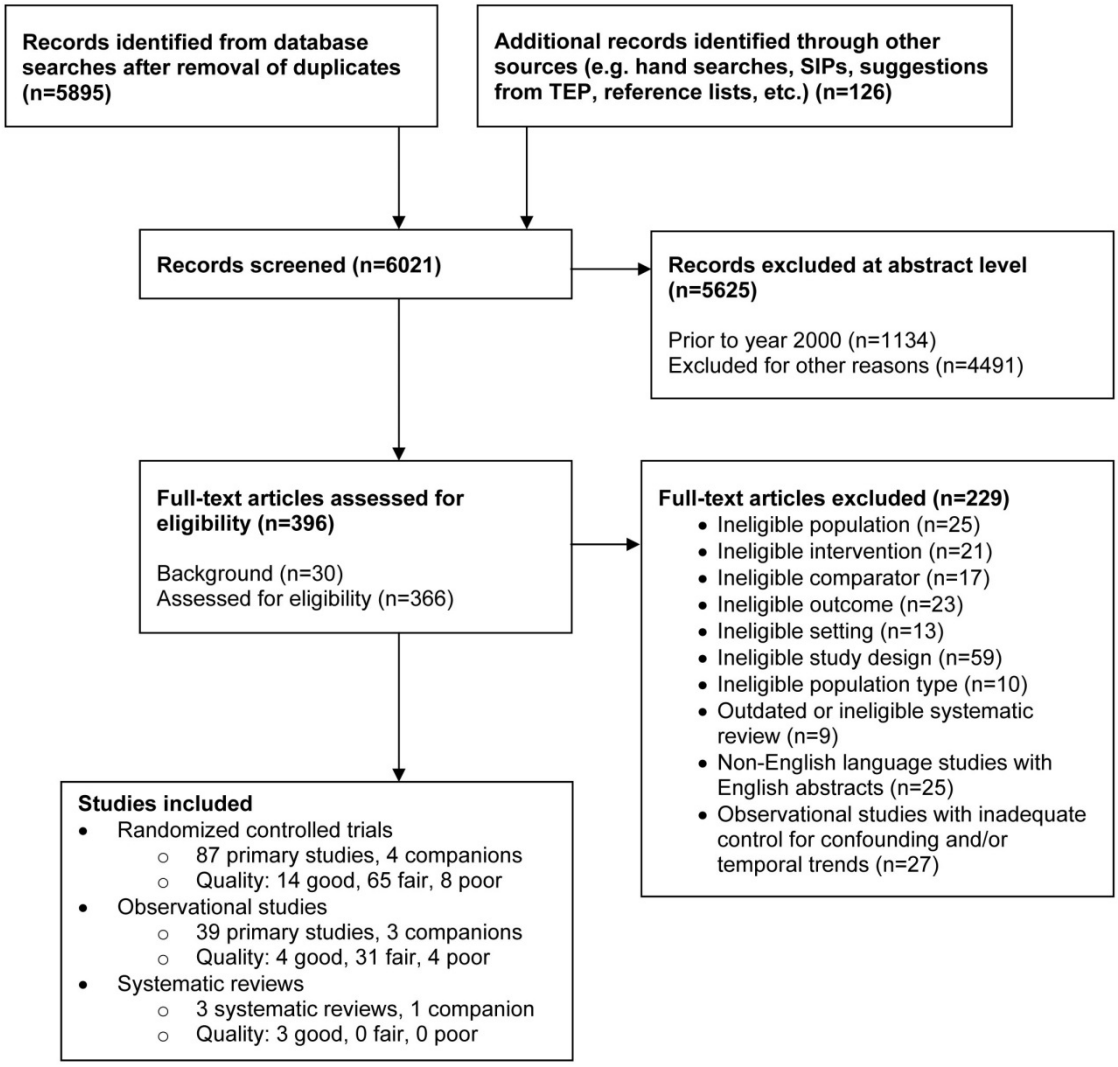
Peer Review and Public Commentary

The draft report will be posted on the AHRQ Web site for 4 weeks to obtain public comments. A disposition of comments with authors' responses to the comments will be posted after publication of the final Comparative Effectiveness Review on the public Web site.

Results

The results of our searches and the selection of articles are summarized in the study flow diagram (Figure B). Our comprehensive searches resulted in 6,021 potentially relevant articles. After a dual review of abstracts, 396 articles were retrieved and assessed for eligibility at full-text dual review. Of those, a total of 129 studies (including 87 RCTs, 37 observational studies, and 3 systematic reviews in 137 publications) met inclusion criteria and are included in this report.

Figure B. Results of literature searches[a]



[a] Modified version of PRISMA flow chart by Liberati 2009[18]

Key Findings and Strength of Evidence

The key findings of this review for comparisons of interventions to usual care and head-to-head comparisons of different interventions are separately described in the in summary of evidence tables C and D below. The factors used to determine the overall strength of evidence grades are summarized in Appendix J. We included 133 unique randomized controlled trials and observational studies, most of which were fair quality. The lack of evidence on both the most important benefits and harms prevented assessment of the net benefit of most intervention types. **Appropriate** prescribing was only evaluated in 9 studies and **resistance** was only evaluated in one study. For appropriate prescribing, although we sought to assess whether the definition of appropriateness affects the apparent effectiveness of interventions, this was not possible due to the potential confounding influences of a wide variety of other factors. For all outcomes, although we sought to determine whether strategies differed based on various patient, clinical, and contextual factors, this was also not possible for the same reason.

Comparisons to Usual Care

Table C summarizes evidence across outcomes for each intervention compared with usual care. Four intervention types stood out as having the best evidence because they were the only ones that found benefit for resistance or appropriate prescribing: **(1) Watchful waiting** was the only intervention that had any evidence of reducing **resistance** to 4-6 antibiotics compared with immediate prescribing (28% vs 56%; $P<0.02$); however, it is low strength (1 RCT, N=223) and limited to children with acute otitis media (AOM). Various other types of delayed prescribing approaches also resulted in lower rates of antibiotic **use** compared with immediate prescribing (absolute difference, range, -63% to -76%; 6 RCTs; N=1664), without any worsening of complications or other clinical outcomes, but the comparison to immediate prescribing limits generalizability of the above findings; **(2) Electronic Decision Support** had moderate-strength evidence of reducing **inappropriate** prescribing in acute bronchitis and AOM (range, -13% to -24%; 2 RCTs, N=12195), low-strength evidence that overall prescribing is reduced when there is adequate use (>50%) of the system, and low-strength evidence of no worsening of healthcare utilization or complications; **(3) Two combined clinic-based education interventions** that targeted patients, parents, and clinicians had low-strength evidence of reducing **inappropriate** prescribing in children with pharyngitis and in adults with sinusitis (-10% to -27%; 1 RCT, 1 observational, N=2193); and **(4) A multi-faceted intervention that combined a clinical algorithm, clinical tutor training , and a 3-part provider education** had low-strength evidence of improving **appropriate** prescribing in patients with acute RTI in Mexico (+21.5%; 1 observational; N=1495), but its net benefit is unknown because its effects on complications and other clinical outcomes were not reported. The next tier of best evidence was for interventions with the highest reductions in overall prescriptions with no important consequences. For this next tier, procalcitonin stood out with the strongest evidence of reducing overall antibiotic prescribing for adults (absolute difference range, -12% to -72%; moderate strength; 5 RCTs; N=2820), with no impact on mortality. In contrast, four interventions that have proved to lack benefit in reducing overall prescriptions include public campaigns targeting adults, a sore throat decision rule, and procalcitonin and rapid viral testing in children.

Table C. Outcomes for each intervention compared with usual care in mixed populations unless otherwise noted

Intervention	Appropriate Prescribing, Resistance	Overall Prescribing	Complications and Other Clinical Outcomes	Knowledge, SDM, Clinician Skills, Time Burden
Education				
Clinic-based: Parents	No evidence	Effective for any acute RTI for age ≤ 14 y (L)	No worsening of return visits for index acute RTI (L)	Improved knowledge in short-term (L)
Clinic-based: Clinicians	No evidence	Small reductions for acute RTIs, upper RTI and AOM, but not acute sinusitis or pharyngitis (L)	Unknown; no evidence	No evidence
Clinic-based: Combined patient, parent, clinician	Improved prescribing in pharyngitis in children and sinusitis in adults (L); no evidence on resistance	Modest reduction for acute RTI (M)	No worsening of AOM complications or of patient or parent satisfaction for acute RTI (L)	No evidence

Intervention	Appropriate Prescribing, Resistance	Overall Prescribing	Complications and Other Clinical Outcomes	Knowledge, SDM, Clinician Skills, Time Burden
Community-based: Parents	No evidence	Moderately reduced for AOM (L)	No worsening of acute RTI complications (L)	Inconclusive evidence
Community-based: Adults	No evidence	Not effective (L)	Unknown; no evidence	Inconclusive evidence
Communication				
Communication	No evidence	Moderate to large reduction for acute RTIs (M)	No worsening of acute RTI complications (L). Inconclusive for reconsultation, symptom improvement, patient satisfaction, or physical or mental quality of life	Inconclusive
Clinical Interventions				
Delayed vs immediate prescribing	Watchful waiting reduced multi-drug resistance for S pneumonia strains in children with AOM (L); No evidence on appropriate use	Significantly reduced use (L)	No worsening of complications, adverse drug effects or reconsultations and *reduced* diarrhea in AOM; but reduced satisfaction and increased persistence of moderate to severe symptoms	No evidence
Sore throat decision rule vs. usual care	No evidence	No reduction (L)	No evidence	No evidence
CRP vs. usual care	No evidence	Moderate reduction (L)	Greater risk of reconsultation within 4 weeks (L), inconclusive for hospital admissions, symptom improvement and patient satisfaction	Inconclusive for patient knowledge; no evidence for time burden
Procalcitonin vs. usual care	No evidence	Large reduction in adult patients with upper RTI or acute bronchitis presenting to primary care or EDs, and those presenting to primary care with upper or lower RTI.	Adults: No worsening of mortality or treatment failure at 30 days in primary care or ED for acute bronchitis, upper RTI, or presenting to primary care with upper or lower acute RTI (L); no worsening in the # of days with limited activity or missing work or continuing symptoms at 28 days post-baseline for upper or lower RTI in primary care Children with suspected AOM: Use of an adult algorithm worsened AEs, but does not worsen composite outcome of AE/lack of efficacy or hospitalizations (L)	
Point-of-care viral testing	No evidence	Not effective in children (L), inconclusive in adults	No evidence	No evidence

Intervention	Appropriate Prescribing, Resistance	Overall Prescribing	Complications and Other Clinical Outcomes	Knowledge, SDM, Clinician Skills, Time Burden
Point-of-care streptococcal antigen testing (rapid strep testing)	Inconclusive for appropriate prescribing; no evidence on resistance	Significant reduction for pharyngitis (L)	No evidence	No evidence
System Level Interventions				
Electronic Decision Support	Improved appropriate prescribing in acute bronchitis and AOM (M). No evidence on resistance	Inconclusive due to mixed findings	No worsening of healthcare utilization or complications (L)	No evidence
Multifaceted Interventions				
Clinical algorithm + clinical tutor training + 3-part provider education	Increased appropriate prescribing (L); no evidence on resistance	No evidence	No evidence	No evidence
Provider education + audit and feedback	No evidence	Not effective in children (L)	Did not decrease patient satisfaction (L)	No evidence
Provider education + delayed prescribing + peer academic detailing	No evidence	Inconclusive	No evidence	No evidence
Provider and patient education + practice profiling + academic detailing	No evidence	Reduced in bronchitis (L)	Did not worsen 1-month clinic attendance (L)	No evidence
Provider and patient education + CRP testing	No evidence	Reduced, primarily due to CRP component (L)	No evidence	
Provider communication training + CRP testing	No evidence	Significant reduction (L)	Increased hospitalization; more days of moderately bad symptoms; but similar reconsultation, diagnostic testing use, and days off work (L)	Inconclusive

Head-to-Head Comparisons

No head-to-head trials have directly compared any of the top four interventions identified above that have the best advantages over usual care. Table D below summarizes the findings from studies that compared different interventions between different categories and within categories and those that evaluated augmentation of a primary intervention with a second intervention. Studies that compared different interventions within and between intervention

categories found some differences; but some were of unclear importance. For sore throat, however, use of the FeverPain clinical score may be a better choice over delayed prescribing because it both reduced overall prescriptions and led to one fewer day of moderately bad or worse symptoms.

In the augmentation studies, more was not always better. The best evidence supports use of adding a clinical decision support system to a public education program because the combination improved **appropriate** prescribing (moderate strength), but we still have uncertainly about how it might affect other important outcomes. Multifaceted interventions that include certain POC tests may reduce overall prescribing more than their non-POC components alone, but not the POC-components alone. Adding communication training to clinician education may not be worth the potential additional effort as the combination did not lead to improvements in appropriate or overall prescribing. Adding C-reactive protein (CRP) testing to a clinical algorithm and adding patient education to delayed prescribing have unclear usefulness as available evidence was mostly inconclusive.

Table D. Outcomes for head-to-head comparisons of interventions in mixed populations unless otherwise noted

Intervention	Appropriate Prescribing, Resistance	Overall Prescribing	Complications and Other Clinical Outcomes	Knowledge, SDM, Clinician Skills, Time Burden
Comparisons Between Intervention Categories				
Communication vs CRP	No evidence	Inconclusive	Borderline fewer reconsultations with CRP (L); similar effect on patients' symptoms (L)	No evidence
Comparisons Within intervention categories: Clinical				
Different delayed prescribing strategies	No evidence	No differences (L)	Similar complications, diarrhea or rash, duration of moderately bad symptoms, reconsultations, or satisfaction; but vomiting and abdominal pain highest with giving prescriptions with instructions to delay (L)	No evidence
Delayed prescribing vs. clinical score	No evidence	Greater reduction with FeverPAIN score use in sore throat (L)	Similar return visits, but delayed prescribing leads to an additional day of moderately bad or worse symptoms in patients with sore throat	No evidence
Augmentation				
CRP plus clinical algorithm vs. algorithm alone	No evidence	Inconclusive	Inconclusive	
Enhanced provider communication + CRP vs each alone	No evidence	Lower than communication training alone but not CRP alone, particularly those with LRTIs. (L)	Similar hospitalization, median number of days of moderately bad symptoms, reconsultation rates, diagnostic testing use and days off work (L)	Combination had highest time burden (L)

Intervention	Appropriate Prescribing, Resistance	Overall Prescribing	Complications and Other Clinical Outcomes	Knowledge, SDM, Clinician Skills, Time Burden
Combining rapid strep testing plus a decision rule vs. various comparators	No evidence	Lower than delayed prescribing, the decision rule alone, but not rapid strep testing alone in sore throat (L)	Similar symptom improvements and return visits (L)	No evidence
Adding a clinical decision support system to a public education campaign	Improved appropriate prescribing (M); no evidence on resistance	No evidence	No evidence	No evidence
Adding communication training to clinician education	No improvement in *appropriate* prescribing (L); no evidence on resistance	No improvement in *overall* prescribing (L)	Inconclusive	No evidence
Adding patient education materials (e.g., leaflets) to a delayed prescribing strategy	Inconclusive	No evidence	More clinic visits (L)	No evidence

Findings in Relationship to What is Already Known

Several systematic reviews of interventions to improve appropriate prescribing have been conducted previously, but none included the full range of outcomes addressed in this review. In contrast to our identification of (1) delayed prescribing, (2) Electronic Decision Support, (3) clinic-based education programs that target patients, parents and clinicians and (4) a multi-faceted intervention that combined a clinical algorithm, clinical tutor training, and a 3-part provider education as the top 4 interventions with the strongest evidence of effectiveness, previous reviews more broadly concluded that multifaceted educational interventions, clinician education, and delayed prescribing may be more effective in certain settings. These reviews come to differing conclusions compared with our report for multiple reasons, including the addition of a large volume of newer evidence, the use of a formal system to grade the strength of the evidence, and the scope of interventions considered (e.g., point-of-care tests).

Specific interventions that have been recommended by professional organizations and societies include delayed prescribing for children with nonsevere symptoms and persistent sinusitis (American Academy of Pediatrics), patient and family education for uncomplicated acute bronchitis (Michigan Quality Improvement Consortium [MQIC] and the American College of Chest Physicians), and rapid strep testing for pharyngitis (MQIC and the Infectious Disease Society of America). Our findings generally support these recommendations, but go further in identifying electronic decision support and procalcitonin as additional measures with evidence of benefit.

Applicability

Table E below summarizes the applicability of the evidence within the elements of the PICOTS framework.

Table E. Summary of applicability

Element	Details
Population	
Patients	Mean age 26 years with any acute RTI or specific infections of pharyngitis (including 'sore throat' and tonsillitis) and acute otitis media
Clinicians	General practice or primary care
Intervention	
Education	Varied widely in method, duration, intensity and local tailoring
Communication	Varied from in-person to online methods and varied in intensity and duration
Delayed prescribing	Methods varied widely from leaving the decision to the patient, requiring the patient to return to the clinic, or other methods
Point-of-care testing	CRP algorithms varied across studies. Procalcitonin algorithms were consistent across studies. Rapid viral tests included one that was multiviral and the rest were specific for influenza. When reported diagnostic accuracy was consistent for rapid viral and strep tests.
System level	Computer decision support tools were somewhat variable, with some requiring active clinician access, while others used a 'pop-up' screen
Multifaceted	Most often included some form of education and/or communication training combined with other interventions.
Comparators	Most often usual care, except most studies of delayed prescribing compared to immediate or no prescribing. There were few head-to-head trials of competing interventions.
Outcomes	Most studies focused on overall prescribing, with few studies reporting on appropriate prescribing and resistance or on the clinical consequences of reduced prescribing. Those that did used inconsistent definitions and methods
Timeframes and settings	Only 45% of studies were conducted in the US, potentially seriously limiting the applicability of the evidence due to variation in baseline prescribing rates and healthcare systems, cultural attitudes and clinical and patient behaviors and expectations. Most studies evaluated outcomes only over a single season. Community-based education programs is the only intervention type that evaluated outcomes over multiple seasons, allowing for evaluation of sustainability

Implications for Clinical and Policy Decisionmaking

In an effort to improve appropriate prescribing of antibiotics for acute RTIs, clinicians and policymakers need to make choices among the relevant interventions based on the best evidence. With the ultimate goal being reduction in antibiotic resistance, the best evidence to date is for using a delayed prescribing or watchful waiting approach. Although delayed prescribing has mainly been compared to interventions that do not reflect usual care, it has been shown to result in less resistance to antibiotics, to be effective in reducing overall antibiotic use and is easily implementable. While it seems clear that patients will experience symptoms longer and will have lower satisfaction compared with receiving a prescription immediately, comparison to usual care where there would be a mix of immediate, delayed, or no prescribing may result in fewer differences.

The next tier of best evidence is interventions shown to improve appropriate prescribing. These include patient and combined patient and clinician education programs. Patient education can be simple, for example, waiting room posters featuring a letter from a local clinician. Clinician education programs should be locally tailored and the balance of program intensity and clinician participation needs to be taken into consideration. Electronic decision support systems have been show to improve prescribing for bronchitis and acute otitis media and may be easily implementable in electronic medical record systems. The resources required to initiate the program and for clinicians to use such systems has not been studied. Multifaceted interventions shown to improve appropriate prescribing are those that involve an electronic decision support system combined with public education campaigns for parents, and a program combining a clinical algorithm with clinician education. Unfortunately there is no good evidence on the

relative sustainability of these interventions. Even the comparison across the interventions or the combining of them for synergy is less well studied than is needed.

While the evidence on rapid strep tests, procalcitonin and CRP was limited to overall antibiotic use and other secondary outcomes, these interventions appear to hold promise, as the reductions in overall prescribing can be larger than with other interventions. Evidence does not support the regular use of viral testing as a way to improve appropriate prescribing of antibiotics at this time. The reasons for this finding may be multifactorial and may include test accuracy limitations. For both CRP and procalcitonin, implementation is restricted somewhat by the limitations of the current algorithms used to guide clinicians. With CRP, there is a lack of standardization across the algorithms in terms of consistent guidance for clinicians on how to interpret and act on the test results such that it cannot be recommended for standard use at this time. For procalcitonin, while there is agreement across algorithms in terms of thresholds for antibiotic use, they were developed for use in adults and use in children led to increased antibiotic use. For all the of the point-of-care tests, additional work is need to evaluate the tradeoffs in resource use required, specific populations where they are best used, and their sustainability as an intervention.

Limitations of the Review Process

Potential limitations in our process include the exclusion of non-English language publications, our literature search strategies, and exclusion of observational studies that did not either control for potential confounding, or were simple before-after studies without a time-series design. Examination of the non-English studies with English abstracts did not identify any inconsistencies or additional interventions. Because there are no standard search terms that uniformly cover all interventions and outcomes of interest, it is possible we were unable to identify all potentially relevant studies. Our TEP members and reference lists of previously published systematic reviews were particularly useful in identifying additional citations for consideration. Although we imposed limitations on observational studies based on control for confounding, we attempted to minimize our potential for missing important studies by allowing for any form of controlling for confounding, including simple stratification of results by potential confounders.

Gaps in the Evidence Base

The biggest gap in evidence is in outcome reporting in general. Most studies focused on overall prescribing, with few studies reporting on **appropriate** prescribing and resistance or on the clinical consequences of reduced prescribing. Those that did used inconsistent definitions and methods. For overall prescribing outcomes, our ability to judge the meaningfulness of the reductions was limited due to a general lack of established minimally important difference parameters. We also could not assess how to optimize use of effective interventions due to the lack of sufficient detail on potential effect modifiers (e.g., patient, clinician, setting characteristics). For the multifaceted intervention category, which may hold the key to effectiveness, their consistency is largely unknown and collectively they do not provide a cohesive picture of effectiveness because most represent a “one-off” intervention with enough variation that we could not combine them. Finally, with only 45 percent of studies conducted in the United States, there is potentially a gap in the applicability of the available evidence to US settings.

Future Research Needs

Based on the gaps and weaknesses identified through the systematic review of the literature, the following areas present an opportunity for new research to support healthcare decisions. Studies of interventions to improve appropriate antibiotic prescribing in acute RTIs should have the following methodological features:

- Most studies in this area can be randomized and in such cases cluster randomization should be used.
- Nonrandomized studies must adhere to the best methods, particularly using methods to control for potential confounding.
- Interventions and comparators should be competing interventions from the best identified in this report.
- Interventions that involve changing behavior (e.g., educational and communication interventions) should be created based on the best evidence to date rather than designing a new intervention each time.
- Define appropriate prescribing and use. The definition needs to be clinically defensible, the ascertainment of this outcome needs to include some level of chart review, and the measurement of actual use needs to be considered.
- Measure resistance as an outcome.
- Measure clinical outcomes and adverse consequences of the competing interventions.
- Background contextual factors must be reported and considered, particularly baseline prescribing rates for particular acute RTIs.
- Patient and provider characteristics should be analyzed as effect modifiers.

Conclusions

Despite the enormous research efforts over the past two decades (129 studies in 137 publications, including 91 RCTs), the evidence is still largely inadequate to identify optimum intervention strategies for improving appropriate antibiotic use for acute RTIs, due to a lack of evidence on both the most important benefits and harms, preventing assessment of net benefit. Most studies focused on overall antibiotic use and other intermediate clinical outcomes and not the most important outcomes of appropriate prescription and use of antibiotics and antibiotic resistance. While most interventions had at least low-strength evidence of reducing overall prescribing, the best evidence available supports the use of electronic decision support systems and educational strategies because they have the strongest evidence (moderate strength) of an improvement in *appropriate* prescribing and at least low-strength evidence that electronic decision support systems do not increase complication rates and educational interventions do not lead to a worsening of clinical outcomes. There is moderate strength evidence that use of both procalcitonin and CRP point-of-care diagnostic tests reduce overall prescribing and evidence of no impact on mortality with procalcitonin and no increase in return clinic visits or symptom worsening with CRP versus communication training. Rapid strep testing and communication training for clinicians both have moderate strength evidence of reducing overall prescribing, but lack evidence for other outcomes. Delayed prescribing is the only intervention with evidence of lower rates of antibiotic *use* (low strength). In children, procalcitonin and rapid viral testing did not improve overall antibiotic prescribing. Future studies need to have rigorous design, assess appropriate prescribing and resistance to antibiotics, and evaluate the impact of important

potential effect modifiers, such as background prescribing rates and clinician or patient characteristics.

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Introduction

Inappropriate Use of Antibiotics, Development of Resistance, and Other Consequences

Antibiotics transformed the practice of medicine in the last half of the 20th century. Penicillin was even considered by many to be a sort of miracle drug. Beginning in the 1940s, antibiotics seemed to be the key to the inevitable elimination of infectious disease as a serious public health problem. With antibiotics, common infections and injuries that would previously have caused death or debility could now be effectively treated and cured. Due to their exquisite adaptability, however, bacteria have a great capacity to develop resistance to antibiotics and the problem of resistant strains of bacteria has grown substantially. In the United States each year, at least 2 million people acquire infections with antibiotic-resistant bacteria and 23,000 people die of such infections.[1] For decades, there has been increasing awareness that using antibiotics to treat nonbacterial and/or benign self-limiting illnesses contributes to the development of antibiotic-resistant bacteria[2-4] and may be the most important factor in the development of antibiotic resistance.[1] Reducing inappropriate antibiotic use is, therefore, critical to arresting the growing prevalence of antibiotic-resistant bacteria.[5]

In addition to being the chief factor in the development of antibiotic resistance, use of antibiotics where they are not warranted unnecessarily exposes patients to potential adverse side effects and increases medical costs. Recent studies reported in the news have drawn attention to potential adverse effects of antibiotics beyond those more established side effects such as allergic reactions or gastrointestinal disruption. One such report indicated that children with four or more courses of broad-spectrum antibiotics in their first 2 years of life were more likely to be obese later in childhood.[6] Another recent report discussed evidence that certain antibiotics might be associated with increased risks of death and serious cardiac arrhythmias during standard treatment durations.[7] While the reduction of resistant organisms is the principal public health concern motivating efforts to improve appropriate antibiotic use, findings of this sort underscore the additional possible benefits of reductions in adverse effects and medical costs.

Inappropriate Use of Antibiotics and Acute Respiratory Tract Infections

Acute respiratory tract infections (RTIs) account for approximately 70 percent of primary diagnoses in adults presenting for ambulatory care office visits with a chief symptom of cough.[8] Acute RTIs include acute bronchitis, acute otitis media (AOM), pharyngitis/tonsillitis, rhinitis, sinusitis, and other viral syndromes.[9] Standard recommended management of acute RTIs is to focus on ruling out serious illness for which antibiotics are indicated, such as bacterial pneumonia, and providing education and symptomatic relief for illnesses that do not require antibiotics. Existing clinical guidelines indicate that acute bronchitis and other acute RTIs that can be caused by either viruses or bacteria, and which are generally self-limiting, should usually not be treated with antibiotics unless certain clinical indications are present.[9] Despite guidelines recommending no antibiotic treatment for most acute RTIs, the majority of outpatient antibiotic prescriptions in the United States are for acute RTIs. In 1998, an estimated 76 million ambulatory office visits for acute RTIs resulted in 41 million antibiotic prescriptions.[10] A 2013 report regarding healthy adults visiting outpatient offices and emergency departments (EDs) for acute bronchitis revealed prescriptions for antibiotics were given at 73 percent of visits between 1996 and 2010,[11] despite the fact that the majority of acute bronchitis cases are caused by viral pathogens for which antibiotics are not helpful. Clearly, there is a need to identify and promote

strategies that can help to bring antibiotic use for RTIs in line with current evidence-based guidelines.

Reasons For Inappropriate Use and Development of Strategies To Improve Problems

The reasons for inappropriate use of antibiotics for acute RTIs are numerous, diverse, complex, and not well understood. Consequently, strategies to improve appropriate use of antibiotics for RTIs have varied in whose behavior they are designed to change and the means by which they are designed to change that behavior. Strategies may target clinicians who care for patients with acute RTIs in outpatient settings, adult and pediatric patients with acute RTIs, the parents of pediatric patients with acute RTIs, healthy adults and/or children in the general population without a current RTI, or groups whose attendance policies may indirectly affect the use of antibiotics (e.g., employers, school officials). Interventions may also fall into any of several categories. *Educational strategies* include educating clinicians about current treatment guidelines or providing information to patients or parents of patients about why antibiotic treatment is not recommended. *Strategies to improve communication* between clinicians and patients include interventions designed to improve shared decisionmaking around use of antibiotics for acute RTIs. *Clinical strategies* include delayed prescribing of antibiotics or use of point-of-care diagnostic tests (e.g., rapid strep). *System level strategies* include clinician reminders (paper-based or electronic), clinician audit and feedback, and financial or regulatory incentives for clinicians or patients. Furthermore, *multifaceted* approaches may include numerous elements of one or more of the aforementioned strategies.

Important Outcomes For Measuring Effectiveness of Interventions To Improve Appropriate Antibiotic Use

In evaluating interventions to improve appropriate prescribing and use of antibiotics, the most direct outcomes of interest are changes in appropriate prescribing and use. Although clinical guidelines identify the principles of appropriate prescribing for acute RTIs, making the determination on a case-by-case basis can be difficult. There is also not consensus on how to measure appropriate prescribing as an outcome. Therefore it is important to capture how each study defines and measures appropriateness, and to find intermediate or proxy outcomes for those studies that do not. Given that studies find that half or more of antibiotic prescriptions for various RTIs are not necessary,[5,12,13] measures of overall change in antibiotic prescription or use are a relevant, albeit limited, proxy for changes in appropriate use. The usefulness of overall prescribing as a proxy for appropriate prescribing may vary based on background factors and we do not know precisely how good of a proxy measure it is because the estimates of the rate of overall prescribing that is inappropriate/appropriate range so widely. For example, one study found a rate of 80% unnecessary prescribing of antibiotics for acute RTI,[12] suggesting overall prescribing is a fairly good proxy for appropriate prescribing, while another study that reported 50% unnecessary prescribing suggests a much lower level of confidence in the proxy measure.[13]

Given that the most important reason for reducing inappropriate use of antibiotics is to curb the development of antibiotic-resistant bacteria, potential effects of interventions on antibiotic resistance is an outcome of interest. In addition, relevant intermediate outcomes include improved knowledge regarding the use of antibiotics for acute RTI and improved shared decisionmaking skills in patients and clinicians.

Interventions to improve appropriate antibiotic use may also have a variety of potentially undesirable outcomes. For example, if efforts to improve appropriate antibiotic use resulted in

under-treatment of patients for whom antibiotics would have been indicated, undesirable outcomes such as medical complications, hospital admissions, and mortality might increase. Similarly, reduced prescription of antibiotics may lead to increased clinic visits, longer duration of symptoms, or longer time to return to school or work. Depending on patients' expectations, patient satisfaction may also be affected. The interventions themselves also may require substantial time and resources. As numerous patient, clinician, and setting factors may modify the comparative effectiveness of interventions to improve appropriate antibiotic use (e.g., type of RTI, patient demographics, clinician specialty, type of clinic, geographic location, etc.), a review of the evidence should seek to clarify whether there are particular subpopulations that are more or less likely to benefit.

Existing Systematic Reviews and Guidelines Addressing Appropriate Antibiotic Use For Acute Respiratory Tract Infections

Although there are a number of existing systematic reviews and guidelines that address the issue of appropriate antibiotic use, they either focus on a single population, intervention, or disease, or else do not cover the evidence currently available. The most comprehensive review to date, a 2006 technical review by Agency for Healthcare Research and Quality (AHRQ), entitled "Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies Volume 4—Antibiotic Prescribing Behavior" concluded that some quality improvement strategies may be moderately effective in reducing inappropriate antibiotic prescription. While no single strategy is clearly superior, the report concludes that clinician education and delayed prescribing may be more effective in certain settings and that interventions targeting prescribing for all acute RTIs may be more effective than those that target a single type of RTI. However, the 2006 AHRQ review is out of date, as are more recent targeted reviews.[14-16] Therefore, the goal of the present systematic evidence review is to assess the comparative effectiveness of a breadth of possible strategies for reducing antibiotic use when not indicated for acute RTIs in adults and children. In addition to providing evidence on the benefits and potential harms of strategies, the review identifies gaps in the literature and suggestions to guide future research.

Scope and Key Questions

The Key Questions and analytic framework used to guide this report are shown below. The analytic framework (Figure 1) illustrates the scope of this review, including the target population, interventions, comparison, and outcomes that were examined in this review.

Key Question 1. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effectiveness of particular strategies in improving the appropriate prescription or use of antibiotics compared with other strategies or standard care?

a) Does the comparative effectiveness of strategies differ according to how appropriateness is defined?
b) Does the comparative effectiveness of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
c) Does the comparative effectiveness of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?

d) Does the comparative effectiveness of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
e) Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
f) Does the comparative effectiveness differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), system level characteristics, or whether the intervention was locally tailored?

Key Question 2. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on antibiotic resistance compared with other strategies or standard care?

a) Does the comparative effect of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
b) Does the comparative effect of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
c) Does the comparative effect of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
d) Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
e) Does the comparative effect differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), whether the intervention was locally tailored, system-level characteristics, or the source of the resistance data (i.e., population vs. study sample)?

Key Question 3. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on medical complications (including mortality, hospitalization and adverse effects of receiving or not receiving antibiotics) compared with other strategies or standard care?

a) Does the comparative effect of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
b) Does the comparative effect of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
c) Does the comparative effect of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?

d) Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
e) Does the comparative effect differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), whether the intervention was locally tailored or system-level characteristics?

Key Question 4. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on other clinical outcomes (e.g., health care utilization, patient satisfaction) compared with other strategies or standard care?

a) Does the comparative effect of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
b) Does the comparative effect of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
c) Does the comparative effect of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
d) Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
e) Does the comparative effect differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), whether the intervention was locally tailored or system-level characteristics?

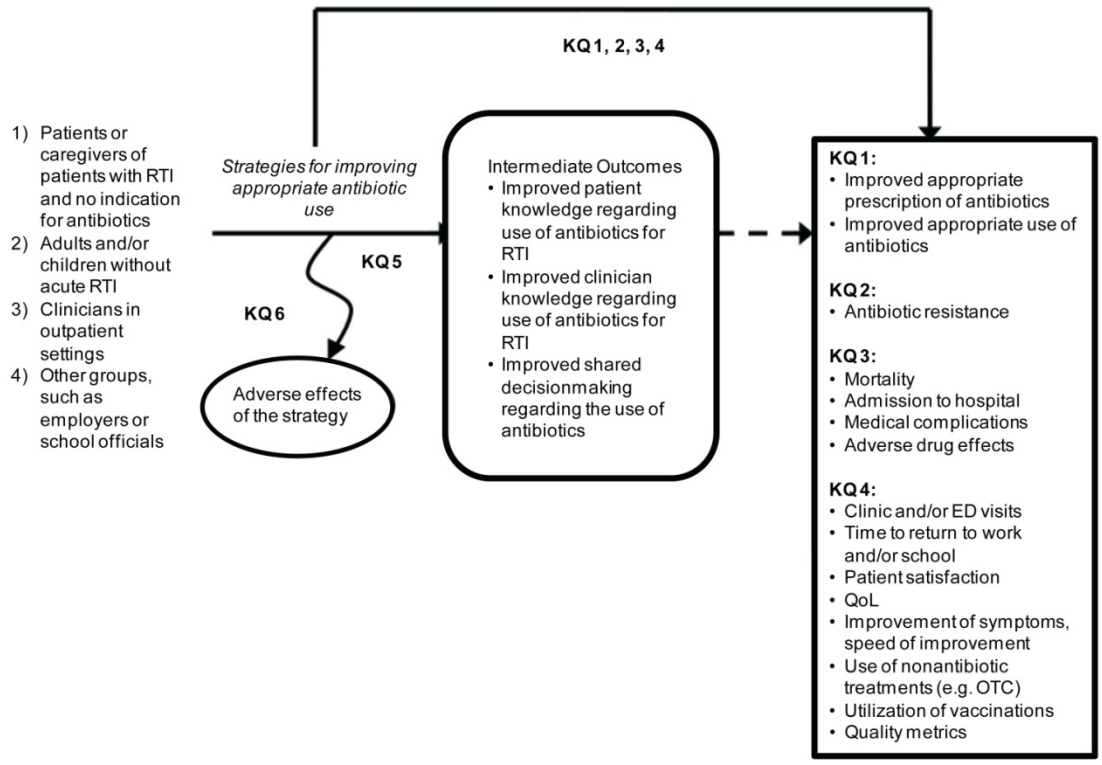
Key Question 5. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on achieving intended intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute respiratory tract infections (clinicians and/or patients), improved shared decisionmaking regarding the use of antibiotics, and improved clinician skills for appropriate antibiotic use (e.g., communication appropriate for patients' literacy level and/or cultural background)?

Key Question 6. What are the comparative nonclinical adverse effects of strategies for improving the appropriate use of antibiotics for acute respiratory tract infections (e.g., increased time burden on clinicians, patients, clinic staff)?

Analytic Framework

The analytic framework below (Figure 1) illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis and their relationship to the Key Questions.

Figure 1. Analytic framework for improving appropriate antibiotic use for acute respiratory tract infections



RTI=respiratory tract infection, ED=emergency department, QOL=quality of life, OTC=over-the-counter

Organization of This Report

For each Key Question, results are organized into subsections for each intervention category. We arranged the subsections to match the ordering of the intervention categories as listed in the inclusion criteria. Within each intervention category subsection, evidence was further grouped by specific intervention type (i.e., delayed prescribing, specific point-of-care tests for the clinical section) and ordered based on volume of evidence (most to least).

Methods

This comparative effectiveness review (CER) follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[17] The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the PRISMA checklist.[18] All methods were determined a priori in the protocol, which is available at http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1913#8793

Topic Refinement and Review Protocol

The topic was nominated by a diverse group of stakeholders, including patients, clinicians, professional societies, and insurers through an AHRQ-sponsored topic identification exercise. A panel of Key Informants gave input on the Key Questions to be examined; these Key Questions were posted on AHRQ's Effective Health Care (EHC) Web site for public comment in January 2015 for 3 weeks and revised in response to comments. We then drafted a protocol for the systematic review and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review. The finalized protocol is posted on the EHC Web site at http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1913#8793. The PROSPERO registration is CRD42014010094.

Literature Search Strategy

To identify articles relevant to each Key Question, a medical librarian searched Ovid MEDLINE® In-Process & Other Non-Indexed Citations from 1990 to May 14, 2014, the Cochrane Database of Systematic Reviews (CDSR) from 2005 to March 2014, and the Cochrane Central Register of Controlled Trials (CCRCT) from 1990 to April 2014. Search dates and exact search strings are provided in Appendix A. Gray literature was identified by searching clinical trial registries (ClinicalTrials.gov and WHO Trial Registries). We conducted hand searches for studies included in reference lists of included systematic reviews. Scientific Information Packets were solicited from relevant stakeholders (e.g., manufacturers of point-of-care tests, advocacy groups, professional societies, large healthcare organizations, etc.) through the Scientific Resource Center. The search strategy was reviewed by a second medical librarian who provided comments to improve the strategy. Literature searches will be updated while the draft report is out for external review.

Inclusion and Exclusion Criteria

Studies were included based on the population, intervention, comparator, outcomes, timing, settings, and study designs (PICOTS) detailed below (Table 1a). Based on input from our Technical Expert Panel (TEP), and as we recognized that the 1990s mark the decade when many organizations, such as the Centers for Disease Control and Prevention, initiated formal efforts to promote appropriate antibiotic use, the Pacific Northwest Evidence-based Practice Center (PNW EPC) restricted inclusion to studies published since 1990. Given the existence of good systematic reviews after 2000, and information from our TEP that there are few relevant studies before 2000, we identified studies published from 1990 to 2000 through systematic reviews of the topic,

with confirmation by the TEP that nothing important had been missed. Primary literature published from 2000 onward was identified through primary literature searches. Due to resource limitations, we only included studies published in English. Studies published in other languages but otherwise appearing to be eligible based on the title or English-language abstract were identified and reviewed in order to evaluate potential language bias.

Table 1a. Criteria for eligibility based on PICOTS framework

PICOTS	Criteria for Eligibility
Populations	Adult and pediatric patients with an acute RTI and no clear indication for antibiotic treatment. RTOs of interest include: acute bronchitis, AOM, sore throat/pharyngitis/tonsillitis, rhinitis, sinusitis, cough, and common cold.[6] Parents of pediatric patients with acute RTI and no clear indication for antibiotic treatment. Healthy adults and/or children without a current acute RTI, who may develop an acute RTI in the future. Clinicians and others who care for patients with acute RTI in outpatient settings. Groups whose attendance policies may indirectly affect the use of antibiotics, such as employers or school officials
Interventions	Any strategy for improving appropriate use of antibiotics when not indicated for acute RTI, which fall into various categories, including: Educational, behavioral and psychological interventions that target clinicians, patients, or both. Strategies to improve communication between clinicians and patients, such as those designed to improve shared decisionmaking. Clinical strategies such as delayed prescribing of antibiotics, clinical prediction rules, use of risk assessment or diagnostic prediction, use of nonantibiotic alternatives, or use of relevant point-of-care diagnostic tests. Any point-of-care test that is available and used in primary care settings for diagnostic purposes with the ability to provide results within a reasonable period of time (e.g. during the clinic visit). Examples include inflammatory tests (e.g., procalcitonin, CRP, white blood cell, etc.), rapid multiplex PCR tests used to rule in/out organisms (e.g. rapid strep test, influenza, RSV), and routine diagnostic tests, such as chest x-ray, pulse oximetry, and blood gasses, when they are specifically evaluated as an intervention for improving antibiotic use. System level strategies such as clinician reminders (paper-based or electronic), clinician audit and feedback, financial or regulatory incentives for clinicians or patients, antimicrobial stewardship programs, and pharmacist review. Multifaceted approaches that include numerous elements of one or more of the above strategies
Comparators	Different strategies for improving appropriate use of antibiotics when not indicated for acute RTI. Standard care without a strategy for improving appropriate use of antibiotics

PICOTS	Criteria for Eligibility
Outcomes	**Key Question 1** Increased appropriate prescription of antibiotics (primary outcome). Increased appropriate use of antibiotics (primary outcome). **Key Question 2** Antibiotic resistance. **Key Question 3** Mortality. Admission to hospital. Medical complications. Adverse drug effects, including *clostridium difficile* infections. **Key Question 4** Clinic visits (index, return and subsequent episodes), ED visits. Time to return to work and/or school. Patient satisfaction Quality of life. Improvement in patient symptoms, speed of improvement. Use of nonantibiotic treatments, such as over-the-counter medications. **Key Question 5** Intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute RTI (clinician and/or patient), or improved shared decisionmaking. **Key Question 6** Adverse effects of the strategy, such as increased time burden on clinicians, sustainability of intervention (e.g. measures of continued effectiveness over time), diagnostic resource use associated with point-of-care testing, diagnostic coding (e.g., ICD billing codes) according to desired action (prescribe/not prescribe).
Timing	Any duration of followup was eligible
Setting	Outpatient care settings including institutional settings, emergency care settings and other settings, such as school or workplace
Study Designs	Systematic Reviews with similar scope and search dates within past 3 years. RCTs Prospective and retrospective cohort studies including database studies For areas in which such direct comparative evidence is lacking, we included before-after studies that used methods to control for potential confounding and studies with a time-series design that evaluated temporal trends.

CRP = C-reactive protein; ED = emergency department; PCR = polymerase chain reaction; RCT = randomized controlled trial; RTI = respiratory tract infection

Study Selection

Study selection followed AHRQ guidance for reducing bias.[19,20] Abstracts for citations identified through searches were screened for eligibility by one reviewer, with any deemed ineligible reviewed by a second reviewer. Full text of all citations deemed potentially eligible for inclusion by at least one reviewer were obtained for further evaluation. Full-text articles were reviewed by two reviewers, with differences in judgment on eligibility resolved through consensus or inclusion of a third party.

Results published only in abstract form were not included because inadequate details were available for assessing quality. Protocols for RCTs were included to inform quality assessment of completed trials or to speak to the potential of future research. In general, at full-text level, studies were excluded for one or more of the following reasons: ineligible population, ineligible intervention, ineligible comparator, ineligible outcome, ineligible setting (e.g., inpatient), ineligible study design (e.g., case report, qualitative methods), ineligible publication type (e.g. editorial, letter, narrative review), outdated or ineligible systematic review, or non-English language.

All citations were entered in an electronic database (Endnote® X7, Thomson Reuters) and screening decisions for each citation were also tracked in the database. Appendix B lists all studies included at full text, while all studies excluded at full text are listed in Appendix C.

Data Extraction

The following data were abstracted from included studies: study design, number of participants randomized or enrolled, patient and provider population criteria, intervention strategy and comparator characteristics, patient characteristics (e.g., type of RTI, signs and symptoms, duration of illness, age, ethnicity, and socioeconomic status), provider characteristics (e.g., specialty, number of years in practice, and type of clinic), background contextual factors (e.g., time of year, and patterns of disease activity), definition of appropriate antibiotic use, and results for each outcome. One reviewer abstracted study data, and a second reviewer appraised the abstractions. Intention-to-treat results were recorded if available. We considered potential effect modifiers or sources of heterogeneity, which are listed in Table 1b below. Appendixes D, F, and H contain evidence tables for data abstraction of RCTs, observational studies, and systematic reviews. Studies are organized in alphabetical order by primary author name.

Table 1b. Potential sources of heterogeneity

Category	Sources of Heterogeneity
Populations	Type of RTI, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior RTIs, and prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained
Interventions	Clinician characteristics: Specialty, number of years in practice, type of clinic organization, geographic region, and population served Diagnostic method or definition used Clinician's perception of the patient's illness severity Clinician's diagnostic certainty Local tailoring Accuracy of diagnostic tests
Outcomes	Appropriate prescription/use: Definition of appropriateness Antibiotic resistance: Data source (i.e., population vs. study sample)
Setting	Time of year; during a disease epidemic or outbreak period

RTI=respiratory tract infection

Quality (Risk of Bias) Assessment of Individual Studies

The internal validity (quality) of systematic reviews, RCTs, and observational studies were assessed based on predefined criteria established by the Drug Effectiveness Review Project.[21] For trials, these criteria were based initially on the criteria used by the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom).[22,23] In rating the internal validity of trials, we evaluated methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; adequate reporting of dropouts, attrition, loss to followup; and the use of intention-to-treat analysis.

The internal validity of observational studies were rated based on criteria specific to these study designs: the adequacy of the patient selection process, whether there was important differential loss to followup or overall high loss to followup, the adequacy of event ascertainment, whether acceptable statistical techniques were used to minimize potential confounding factors, and whether the duration of followup was reasonable to capture investigated events.

All assessments were done at the overall study level and resulted in a rating of good, fair, or poor. We utilized a dual rating procedure for study quality, where all studies were first rated by one reviewer and then checked by another reviewer. All disagreements were resolved using a consensus process.

Data Synthesis

Evidence tables were constructed to illustrate the study characteristics, quality ratings, and results for all included studies (Appendixes D through I). A hierarchy-of-evidence approach was used, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Systematic reviews that had a similar scope to our review were used as primary evidence where possible; where a review included all studies of an intervention, population, and outcome we summarized the findings of the review as our evidence. Where an eligible review did not include all identified studies we noted the review and its findings, but undertook a new synthesis to incorporate the newer studies not included in the review.

Studies varied in how appropriateness was defined or determined. We accepted and recorded any definition of appropriateness. When definition of appropriate was provided, we grouped together studies that use similar definitions of appropriateness and categorized the different groups based on concordance with (e.g., high, medium, low) select clinical practice guidelines (e.g., American Academy of Pediatrics, American College of Chest Physicians, American Academy of Family Physicians). We then evaluated whether the comparative effectiveness of strategies differed across categories. We also found that overall reduction in antibiotic prescription or use was reported, without a determination of appropriateness. While this is not a direct measure of the primary outcomes, we reported these as indirect measures of the impact of the intervention.

Where appropriate, we synthesized outcome data quantitatively using meta-analysis to pool outcomes, with odds ratio as the principle summary measure. To determine the appropriateness of pooling outcomes (e.g., percent reduction in antibiotic prescribing or use) using meta-analysis, the quality of the studies and the heterogeneity among studies in design, population, interventions, and outcomes were considered. Data from high risk of bias studies were generally excluded from the synthesis, except to undertake sensitivity analyses or to note where high risk of bias studies constitute the only evidence for an important outcome. To determine the appropriateness of meta-analysis, we considered the internal validity of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. Appropriate measures were chosen based on the type of data for meta-analysis (e.g., relative risk, odds ratio). The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[24,25] Random-effects models were used to estimate pooled effects.[26] Statistical heterogeneity was explored by using subgroup analysis or meta-regression. Forest plots were used when applicable to graphically summarize the results of individual studies and of the pooled analysis.[27]

When both trial and observational studies were found for a given intervention-outcome pair, trial evidence was given more weight according to the EPC guidance on grading the strength of the evidence.[19] Sensitivity analyses were also conducted where possible to evaluate differing definitions for inappropriate antibiotic use.

Since most data was not suitable for pooling, we largely summarized the data qualitatively. Qualitative synthesis involved grouping studies by similarity of population and/or intervention

characteristics, including the sources of variation or heterogeneity listed above. Studies varied in how appropriateness was defined or determined. We accepted and recorded any definition of appropriateness. For example, since it is not yet clear whether evidence for one RTI type is applicable to another RTI type or a mixed RTI population, we evaluated these bodies of evidence separately. When definition of appropriate antibiotic use and/or prescription were provided, we grouped together studies that used similar definitions of appropriateness and categorized the different groups based on concordance (e.g., high, medium, low) with select clinical practice guidelines (e.g., American Academy of Pediatrics, American College of Clinical Pharmacy, American Academy of Family Physicians). We then evaluated whether the comparative effectiveness of strategies differed across categories. We also found that studies reported an overall reduction in antibiotic prescription and/or use without a determination of appropriateness. While this is not a direct measure of the primary outcomes, we reported these as indirect measures of the impact of the intervention. Appropriate antibiotic use and/or prescription, when measured separately from overall antibiotic use and/or prescription, was considered a direct measure of our outcomes of interest.

The evidence provided limited opportunity to examine potential publication and reporting biases, primarily because there were so few opportunities for meta-analysis and because so few study protocols were available.

Strength of the Body of Evidence

We used methods outlined in chapter 10 of the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews to grade strength of evidence, which is available from the AHRQ Effective Health Care (EHC) Web site at http://effectivehealthcare.ahrq.gov/repFiles/2009_0805_grading.pdf.[19,28] Outcomes selected for grading were those likely to be of considerable importance to users of the report. After consultation with the TEP members, we prioritized the following outcomes: appropriate antibiotic prescription, antibiotic resistance, medical complications, adverse drug effects, admission to hospital, clinic visits (index, return and subsequent episodes), ED visits, improvement in patient symptoms, speed of improvement, patient satisfaction, quality of life, and adverse effects of the intervention.

Domains considered in grading the strength of evidence included study limitations, consistency, directness, precision, and reporting bias. For evaluating precision, we did not assume any minimum important difference for continuous outcomes, as we are not aware of any that have been validated. So, we accepted any delta and assessed optimal information size for each delta separately. Publication bias was assessed following methods outlined in AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[19,28] Selective outcome and analysis reporting bias were assessed during individual study quality assessment, using trial registry protocols where available, and study publication methods where protocols were not available. Based on assessment of these domains, the body of evidence was assigned a strength-of-evidence grade of high, moderate, or low. In cases where evidence did not exist, was sparse, or contained irreconcilable inconsistency, a grade of insufficient evidence was assigned.

Applicability

Applicability was assessed by paying special attention to study eligibility criteria, characteristics of the enrolled population in comparison to the target population, characteristics of the intervention and comparator used in comparison with care models currently in use, and

clinical relevance and timing of the outcome measures. Methods used for assessing applicability are available from the AHRQ EHC Web site at http://www.effectivehealthcare.ahrq.gov/ehc/products/272/603/Methods%20Guide--Atkins--01-01-2011KM.pdf.[29]

Peer Review and Public Commentary

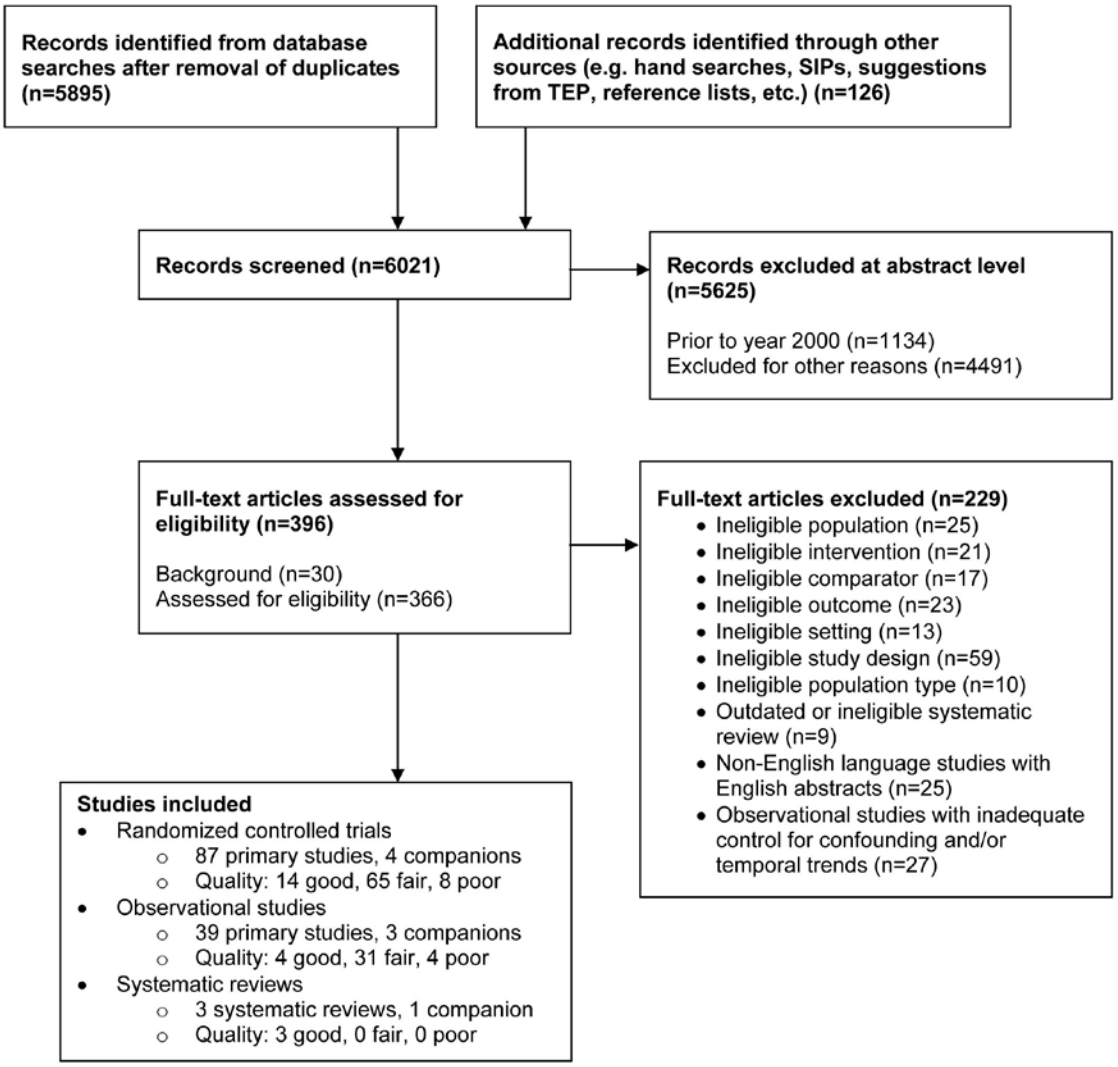
Experts in family medicine, internal medicine, primary care, point-of-care diagnostic testing, clinical pharmacy, infectious disease, epidemiology, and biostatistics were invited to provide peer review of the draft report. The AHRQ Task Order Officer and an EPC Associate Editor will also provide comments and editorial review. The draft report will be posted on the AHRQ Web site for 4 weeks to obtain public comments. A disposition of comments with authors' responses to the peer and public review comments will be posted after publication of the final CER on the public Web site.

Results

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of Ovid MEDLINE®, CDSR®, and CCRCT® yielded 5,895 citations. An additional 126 records were identified by manual searching (hand searches and reference lists) or were suggested by our Technical Expert Panel (TEP). Based on these sources, a total of 6,021 abstracts were screened of which 396 articles were retrieved and assessed for eligibility. Of those, a total of 129 studies: 87 randomized controlled trials (RCTs, 91 publications)],[30-120] 39 observational studies (42 publications),[4,121-161] and 3 systematic reviews (4 publications)[14,162-164]) met inclusion criteria and are included in this report. Of the 137 publications included in this report, 129 were primary study reports[4,14,30-67,70-103,105,107-128,130,131,133-141,143-161,163,164] and 8 were secondary publications.[68,69,104,106,129,132,142,162] Appendix B lists all included studies and Appendix C provides a complete list of articles excluded at full text with the reasons for exclusion.

Figure 2. Results of literature searches[a]



[a] Modified version of PRISMA flow chart by Liberati 2009[165]

Description of Included Studies

Table 2 summarizes the key characteristics of included studies overall and for each of the intervention categories. Educational and clinical intervention strategies were the most widely studied. The majority of studies were multisite RCTs. Most targeted broad populations of children and adults with any acute respiratory tract infection (RTI). Sore throat, pharyngitis, and tonsillitis, were generally the most common RTI types across studies, except that cough was most common in studies of communication interventions. In terms of outcomes, overall antibiotic prescription was the most widely studied, followed by return visits, symptom improvement and patient satisfaction. Antibiotic resistance and quality of life were only reported in 1 study each, and some outcomes (e.g., utilization of vaccinations and quality metrics) were not reported in any studies. The proportion of studies conducted in the United States was 44 percent overall; but this ranged widely across intervention categories, from 12 percent for communication strategies to 69 percent for system-level strategies. Data abstraction tables for all included studies can be found in Appendixes D, F, and H. A complete list of abbreviations for this report can be found at the end of the report. A list of abbreviations specific to the appendixes can be found in Appendix K.

Our internal validity assessments found the majority of studies to be of fair quality. All quality ratings can be found in Appendixes E, G, and I. Our detailed analysis of results focuses on studies with good- or fair-quality ratings. For RCTs, 9 percent were rated poor quality and their main limitations included insufficient detail to assess adequacy of randomization and allocation concealment methods, imbalances at baseline in important patient characteristics, and unacceptably high and differential levels of missing data. A total of 9 percent of observational studies were also rated poor and their main limitations included biased selection and ascertainment methods and uncontrolled confounding.

Due to the heterogeneity among studies in design, population, interventions, and outcomes, there were few occasions where pooling outcomes was appropriate and data were primarily summarized qualitatively. We reported pooled analyses from existing Cochrane reviews on delayed prescribing,[14] procalcitonin,[162,163] and influenza testing.[164] Based on the Methods outlined in Chapter 2, we conducted additional pooled analyses for overall prescription rates for clinic-based education interventions, C-reactive protein (CRP) testing, and rapid strep testing used with a decision rule and for diarrhea and satisfaction for delayed prescribing.

None of the three primary systematic reviews included in this review had conducted strength of evidence (or graded the quality of the evidence).[14,163,164] We assessed strength of evidence for key outcomes based on information provided in the reviews.

Table 2. Characteristics of included randomized controlled trials and observational studies[†]

Study Characteristic	Category	All Studies	Educational	Communication	Clinical and POC	System Level	Multifaceted[a]
Design	RCTs (% Total, % Cluster RCT)	91 (68%, 27%)	37 (65%, 26%)	8 (100%, 88%)	37 (80%, 17%)	8 (62%, 38%)	14 (58%, 25%)
	Observational studies	42 (32%)	20 (35%)	0	9 (20%)	5 (38%)	10 (42%)
	Total (% of all studies)	*133 (100%)*	*57 (43%)*	*8 (6%)*	*46 (35%)*	*13 (10%)*	*24 (18%)*
Comparison	Versus usual care	*111 (83%)*	*55 (96%)*	*3 (37%)*	*31 (67%)*	*12 (92%)*	*15 (62%)*
	Head-to-head	*22 (17%)*	*2 (4%)*	*5 (63%)*	*15 (33%)*	*1 (8%)*	*9 (38%)*
	Total (% of all studies)	*133 (100%)*	*57 (43%)*	*8 (6%)*	*46 (35%)*	*13 (10%)*	*24 (18%)*
Study Quality	Good	18 (14%)	12 (21%)	0	6 (13%)	1 (8%)	2 (8%)
	Fair	103 (77%)	40 (70%)	7 (88%)	38 (83%)	9 (69%)	20 (84%)
	Poor	12 (9%)	5 (9%)	1 (12%)	2 (4%)	3 (23%)	2 (8%)
	Total (% of all studies)	*133 (100%)*	*57 (43%)*	*8 (6%)*	*46 (35%)*	*13 (10%)*	*24 (18%)*
Sample Size	Clinic/Clinician*	110,224	19,300	548	3,297	3,489	84,720
	Patient/Caregiver**	8,777,257	6,821,005	18,092	109,198	592,863	1,504,441
Population	Adult	38 (29%)	13 (23%)	5 (62%)	16 (35%)	3 (23%)	6 (25%)
	Child or both	95 (71%)	44 (77%)	3 (38%)	30 (65%)	10 (77%)	18 (75%)
	Total (% of all studies)	*133 (100%)*	*57 (43%)*	*8 (6%)*	*46 (35%)*	*13 (10%)*	*24 (18%)*
Duration of Intervention	Range	3 w – 4.9 y	1 m – 4 y	5 m – 5 y	3 w – 4 y	6 m – 4 y	3 w – 4.9 y
Duration of followup	Range	1 d – 3.5 y	1 d – 17 m	28 d – 3.5 y	1 d – 3.5 y	2 w – 1 y	1 w – 22 m
Location	United States	59 (44%)	32 (56%)	1 (12%)	11 (24%)	9 (69%)	12 (50%)
	Other	74 (56%)	25 (44%)	7 (88%)	35 (76%)	4 (31%)	12 (50%)
	Total (% of all studies)	*133 (100%)*	*57 (43%)*	*8 (6%)*	*46 (35%)*	*13 (10%)*	*24 (18%)*
Multisite or Single Site***	Multisite	104 (79%)	42 (76%)	8 (100%)	32 (70%)	12 (92%)	23 (96%)
	Single Site	27 (21%)	13 (24%)	0	14 (30%)	1 (8%)	1 (4%)
	Total (% of all studies)	*131 (100%)*	*55 (42%)*	*8 (6%)*	*46 (35%)*	*13 (10%)*	*24 (18%)*
Type of Infection Targeted[‡]	Acute bronchitis	31 (23%)	12 (21%)	1 (12%)	3 (7%)	5 (38%)	12 (50%)
	Acute Otitis media	41 (31%)	20 (35%)	1 (12%)	7 (15%)	6 (46%)	11 (46%)
	Sore throat/pharyngitis/tonsillitis	53 (40%)	20 (35%)	2 (25%)	13 (28%)	8 (62%)	13 (54%)
	Rhinitis	8 (6%)	4 (7%)	1 (12%)	1 (2%)	2 (15%)	2 (8%)
	Sinusitis	27 (20%)	8 (14%)	1 (12%)	4 (9%)	5 (38%)	10 (42%)
	Cough and common cold	25 (19%)	11 (19%)	5 (62%)	10 (22%)	1 (8%)	4 (17%)
	Any Acute RTI	82 (62%)	36 (63%)	6 (75%)	27 (59%)	8 (62%)	14 (58%)
	Total (% of all studies)	*133 (100%)*	*57 (43%)*	*8 (6%)*	*46 (35%)*	*13 (10%)*	*24 (18%)*
Key Question Addressed[‡]	KQ 1 – Appropriate antibiotic prescription or use	109 (82%)	41 (72%)	7 (88%)	39 (85%)	13 (100%)	22 (92%)
	KQ 2 – Antibiotic resistance	1 (1%)	0	0	1 (2%)	0	0
	KQ 3 – Medical complications[b]	18 (14%)	5 (9%)	2 (25%)	12 (26%)	1 (8%)	3 (13%)
	KQ 4 – Other clinical outcomes[c]	65 (49%)	29 (51%)	6 (75%)	25 (54%)	4 (31%)	11 (46%)
	KQ 5 – Intermediate outcomes[d]	15 (11%)	11 (19%)	2 (25%)	1 (2%)	0	1 (4%)
	KQ 6 – Nonclinical adverse events[e]	7 (5%)	2 (4%)	2 (25%)	3 (7%)	2 (15%)	1 (4%)
	Total (% of all studies)	*133 (100%)*	*57 (43%)*	*8 (6%)*	*46 (35%)*	*13 (10%)*	*24 (18%)*

†Note: study counts include both primary and companion studies; studies may be counted in more than one intervention category; column percentages reflect percent of studies in a single intervention category.
[a] Multifaceted is defined as more than one intervention category included in a single arm
[b] Medical complications (e.g. mortality, hospitalization, medical complications, adverse drug effects)
[c] Other clinical outcomes (e.g. clinic and/or ED visits, time to return to work and/or school, patient satisfaction, quality of life, improvement/speed of improvement of symptoms)
[d] Intermediate outcomes (e.g. improved knowledge regarding use of antibiotics for acute RTIs, improved shared decisionmaking and improved clinician skills)
[e] Nonclinical adverse events (e.g. increased time burden on clinicians, patients, clinic staff)
***** Reflects the sum of clinics and healthcare providers
****** Reflects the sum of patients (children and adults), parents of patients, families, patient records, patient visits, and infection episodes
******* Multisite or single site status could not be ascertained from 2 studies of educational interventions.
‡Individual studies often targeted more than one infection type or pertained to more than one Key Question, resulting in sums that exceed total study counts.
KQ = Key Question, POC = point of care, RTI = respiratory tract infection, RCT = randomized controlled trial

Key Question 1. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effectiveness of particular strategies in improving the appropriate prescription or use of antibiotics compared with other strategies or standard care?

Key Points

Educational Interventions

- Low-strength evidence based on 2 good-quality and one fair-quality observational studies suggested that public campaigns aimed at educating parents resulted in moderately reduced overall antibiotic prescribing, particularly for acute otitis media (AOM), but campaigns aimed at adults were not found effective. The effect in prescribing for children may be sustained over several months postintervention.
- Low-strength evidence indicated that clinic-based educational interventions aimed at parents were effective when aimed at a broader age group (up to age 14) for any acute RTI (range of odds ratios 0.39 to 0.76; mean absolute difference 13%).
- Low-strength evidence suggested that educational interventions aimed only at clinicians resulted in small but significant reductions in overall antibiotic prescribing for acute RTIs, prescribing for upper respiratory tract infection (URTI) and AOM, but no difference for acute sinusitis or pharyngitis.
- Moderate-strength evidence suggested that combining patient/parent and clinician education resulted in modest reductions in overall antibiotic prescribing for acute RTI compared with usual care. *Appropriate* prescribing for sinusitis was found increased in one study in adults.

Communication Interventions

- Moderate-strength evidence from five fair-quality trials indicated that interventions to improve communication between clinicians and patients results in moderate to large reduction in overall prescribing of antibiotics for acute RTIs compared with usual care (relative risk range from 0.69 to 0.17).

Clinical Interventions

Delayed Prescribing

- Low-strength evidence suggested that delayed prescribing statistically significantly reduces overall prescription use compared with immediate prescribing.
- Low-strength evidence of no statistically significant differences in overall antibiotic use was found between various strategies of delaying prescribing.

Clinical Scoring Tool

- Low-strength evidence suggested that the FeverPAIN clinical score modestly reduces overall antibiotic use compared with leaving prescriptions for collection in (mostly adult) patients with sore throats.
- Low-strength evidence showed no reduction in overall antibiotic prescriptions with a sore throat decision rule compared with usual care.

Point-of-Care Tests

- CRP point-of-care testing
  - Low-strength evidence suggested that the use of CRP testing results in a moderate reduction in overall prescription and/or use of antibiotics for acute RTI compared with usual care (5 trials, pooled RR 0.69; 95% CI, 0.57 to 0.84)
- Procalcitonin point-of-care testing
  - Moderate-strength evidence indicated that use of a procalcitonin algorithm results in a large reduction (OR 0.1; 95% CI, 0.07 to 0.14) in overall antibiotic prescribing for adult patients with URTI or acute bronchitis presenting to primary care or emergency departments (EDs), and those presenting to primary care with URTI or lower respiratory tract infection (LRTI).
  - Low-strength evidence suggested that in children ages 1 to 18 presenting to an ED with LRTIs, use of an adult procalcitonin algorithm resulted in a significantly greater overall prescribing of antibiotics.
- Point-of-care viral testing
  - Low-strength evidence suggested that point-of-care viral testing for influenza does not significantly decrease overall antibiotic prescribing in children, while evidence in adults was insufficient.
- Point-of-care streptococcal antigen testing (rapid strep testing)
  - There was low-strength evidence that use of point-of-care rapid strep testing results in significantly lower overall antibiotic prescribing for pharyngitis compared with usual care with a wide range in reductions. Evidence for improvement in *appropriate* antibiotic use was insufficient due to sparse evidence.

System-Level Interventions

- There was moderate-strength evidence that electronic decision support systems improve appropriate antibiotic prescribing in acute bronchitis and AOM compared with usual care.
- For electronic decision support systems with at least 50 percent use, there was low-strength evidence of modest reductions (9%) in overall prescribing.

Multifaceted Interventions

Multiple interventions from different categories compared with usual care

- There was low-strength evidence that multifaceted interventions that combine various clinical and provider education components can increase appropriate prescribing by 21.5 percent over usual care in patients with acute RTI.
- There was low-strength evidence that multifaceted interventions that combine provider education and audit and feedback components do not statistically significantly reduce overall antibiotic prescribing for children with acute RTI.
- There was low-strength evidence that multifaceted interventions comprised of four components may statistically significantly reduce overall antibiotic prescriptions compared with usual care, particularly for bronchitis (moderate reductions; range 14% to 22% difference in change).
- There was low-strength evidence based on one trial that the combination of online training in use of CRP and communication skills is superior to communication training alone but not superior to CRP training alone in reducing overall antibiotic prescribing in adults with acute RTI, particularly those with LRTIs.

- There was low-strength evidence that compared with usual care, combining provider and patient education with use of CRP testing leads to a large significant reduction in overall antibiotic prescription across various infection types and that this is largely due to the CRP testing component.
- There was low-strength evidence that rapid strep testing plus a decision rule can achieve lower rates of overall antibiotic prescribing for sore throat than usual care, delayed prescribing, the decision rule alone, but not rapid strep testing alone.

Augmentation: adding a second type of intervention compared with one component alone

- Moderate-strength evidence based on a single large (Patient N = 407,460; Provider N = 334), fair quality trial indicated that adding a clinical decision support system to a community education program on treating acute RTIs in children significantly improves *appropriate* antibiotic prescribing (32% vs. 5%).
- Low-strength evidence from a single trial indicated that adding communication training to clinician education did not improve *appropriate* or overall prescribing.

Detailed Synthesis

Educational Interventions

Education Interventions Aimed at Patients or Parents

Seven studies of an educational intervention strategy for education of patients or parents, four trials and four observational reported the outcome of antibiotic prescribing.[39,57,85,120,121,130,134,147] These studies were mostly good quality. Five focused on educating parents about appropriate use of antibiotics for acute RTIs in their children and 2 were directed at adult patients (see Evidence Tables 1 [Appendix D] and 3 [Appendix F], and Table 3 below). Interventions varied across the study designs, with three evaluating community or national campaigns, and four examining clinic-based interventions. As these were very different approaches (one being more passive and the other being more active), they were considered separately. All of these reported *overall* prescribing of antibiotics.

Clinic-Based Interventions

Low-strength evidence from two fair quality RCTs[85,120] that evaluated simple clinic-based interventions aimed at reducing prescribing for any acute RTI in children (ages 6 months to 14 years) suggested a benefit of the interventions (pooled odds ratio 0.39; 95% CI, 0.26 to 0.58). An observational study (pre-post design) with a similar intervention and patient population found similar results, although not statistically significant, possibly due to lack of statistical power. (Table 3).[121]

A good-quality trial that aimed its intervention only at parents of younger children with AOM provides insufficient evidence to determine an impact on prescribing.[39] In this study (N = 499), parents were given a take-home educational video featuring a clinic pediatrician when the child was healthy (with 2 followup interventions) and measured antibiotic prescribing for AOM or sinusitis over a 12-month period, finding no difference in prescribing compared with the control group (Table 3 below).[39]

Public Campaigns

Three observational studies of public campaigns reported highly variable results, depending in part on the intervention, the comparator, the population (adult or child), outcome measure and how it was ascertained.[130,134,147] Based on these studies we find low-strength evidence that public campaigns reduce antibiotic prescribing significantly in children with acute RTI (particularly for AOM and among those in managed care), but not in adults. Two of these studies, both using comprehensive public campaigns strategies, found reduced prescribing in children with acute RTIs.[130,134] A large study in Colorado found a significant reduction only in children seen in managed care (Table 3). The magnitude of effect appeared to range from 6 to 30 fewer prescriptions per 1000 persons per month (p=0.02). There were no details about specific infections, provider characteristics, or other potential sources of heterogeneity across the studies. Based on several time points before, during the 4-month intervention period and after the campaign, it is clear that the impact of the campaign reached its zenith at 4 months, regardless of which dataset were used (general public vs. managed care) and that there was regression to the mean after the intervention ended in the general and adult managed care groups, but not in the pediatric managed care group. An Israeli study aimed the intervention at parents of young children and found significant reductions in prescriptions for AOM, URTI, and pharyngitis. While all were statistically significant, the reduction for AOM was the largest and the reduction for pharyngitis was very small (see Table 3 below).[134]

A study from England found no impact of a national campaign using only posters advertised in magazines and newspapers, and in some clinics on prescribing of antibiotics for adults with acute RTI. The control group may have had some exposure to the campaign however, and there was guidance published by the National Institute for Clinical Excellence on advising using "delayed prescribing" techniques for acute self-limiting RTIs during the study period. Both of these may have reduced the ability to detect an impact of the campaign.[147] Similarly, the study using a comprehensive public campaigns campaign in Colorado that found an impact in children found no reduction in prescribing for adults with acute RTI treated in managed care, or in estimates of overall antibiotic prescribing in the general public (any reason, any antibiotic) (Table 3).[130]

Outcomes by Subgroups

Assessment of important factors that may contribute to heterogeneity was restricted by the limited reporting of these factors.

Diagnosis. A public campaign intervention in Israel found the greatest effect in reducing prescriptions in children for AOM (OR 0.65; 95% CI, 0.59 to 0.72), with much smaller effects in URTI (OR 0.75; 95% CI, 0.69 to 0.81) or pharyngitis (OR 0.92, 95% CI 0.89 to 0.97).[134] Other studies did not separate results by diagnosis. As noted above, studies of public campaigns did not find any effect in adults, but did find reductions in prescribing for children.[130,147]

Education level. In a study of a brief educational talk by the physician at the time of prescribing a delayed antibiotic approach, the mother's education level was found significantly associated with the decision to give antibiotics ($p<0.05$).[50]

Seasonal effects. A trial of a locally tailored educational video for parents found no impact of the intervention overall, and also found no difference in the results based on winter versus summer time periods.[39]

Local tailoring. All of the RCTs in this group of studies were locally created and tailored interventions, such that pooling of results was not possible. The two public campaigns

interventions that were found effective in reducing prescribing in children involved elements that were locally tailored (e.g., culturally and language appropriate messages based on demographics),[130,134] while the more limited public campaigns intervention aimed at adults did not include such elements.[147]

Table 3. Patient education intervention studies

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Clinic-based Interventions			
Taylor, 2003[39] N = 499 < 24 months AOM or sinusitis Good quality	RCT March 2000 – October 2001 12 mo. followup	Intervention: Take-home video featuring clinic pediatrician; pamphlet followup 6 weeks and 6 months after. Control: Injury prevention pamphlet.	Mean number of antibiotics prescribed per patient diagnosed: AOM: 1.7 vs. 1.9; p=0.23 AOM or sinusitis: 1.9 vs. 2.1; p=0.24
Alder, 2005[120] N = 40 1-10 y, acute RTI Fair quality	RCT August – December 2000	Intervention: Pamphlet and fact sheet. Control: nutrition education	Risk for antibiotic prescription (multiple logistic regression): OR 0.40 (95% CI, 0.08 to 1.92)
Francis, 2009[85] N = 558 6 mo. – 14 y, acute RTI < 7days Good quality	cluster RCT October 2006 – April 2008	Intervention: Interactive book used during visit to foster discussion. Control: Injury prevention pamphlet.	Antibiotics prescribed: 22.2% vs. 42.2% (-20%) OR 0.39 (95% CI, 0.26 to 0.59)
Pshetizky, 2003[50] N = 81 Children 3 mo. – 4 y AOM Good quality	RCT Winter of 1998 – 1999	Intervention: Watchful waiting + brief verbal education during visit. Control: Watchful waiting alone.	Effect of education on antibiotic use: 37% vs. 63% (-26%), p<0.0001 Proportion filling prescription: 40.9% vs. 86.5% (-45.6%) OR 0.11 (95% CI, 0.03 to 0.36)
Ashe, 2006[121] Patient N = 720 6 mo.-10 y, acute RTI Good quality	Pre-Post November – December 2000 vs. 2001	Intervention: Waiting room posters. Control: Preperiod with no intervention.	Prescriptions per consultation: 41.9% vs. 48.6% (-6.7%) OR 0.76 (95% CI, 0.56 to 1.04)
Public Campaigns			
McNulty, 2010[147] Patient N = 1,888 pre and 1,830 post Adults Fair quality	Pre-Post January 2008 vs. 2009	Intervention: The English public antibiotics media campaign. (Advertisements in magazines and newspapers and posters made available to clinics and pharmacies. February 2008.) Control: Scotland (no campaign).	Reported Antibiotic Use (survey) Pre vs. Post Intervention Prescribed an antibiotic: England 34% vs. 35% (+1%), Scotland 29% vs. 35% (+6%) Scotland vs. England: (-5%); p=0.10

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Gonzales, 2008[130] Patient N = 2,686,288 (in 2002) and 2,711,848 (in 2003) Children and adults Good quality	Prospective observational November 2002 – February 2003	Intervention: Mass media campaign in Denver, Colorado based on CDC's Get Smart program. (Billboards, various types bus ads, radio spots. Separate Spanish language interventions. Physician advocacy materials.) Control: Colorado Springs (no campaign).	Change in Antibiotic Prescribing: General population data: no difference, p=0.30 Study MCOs: Pediatric: reduced; p=0.01 Adult: No difference p=0.09
Hemo 2009[134] Patient N = Children with RTI diagnosis 101,401 pre, 84,979 post Good quality	Pre-Post Winter 2004 – 2005 vs. Winter 2005 – 2006	Intervention: A public campaigns campaign in Israel. (Radio and television ads; 4-part television series.) Control: Preintervention winter.	Antibiotic Purchase Rates, OR (95% CI): Children < 18 years with acute RTI URTI: 0.749 (0.694 to 0.808) AOM: 0.652 (0.591 to 0.718) Pharyngitis: 0.931 (0.890 to 0.973)

CDC = Center for Disease Control, MCO = Managed Care Organization, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection

Educational Interventions for Clinicians

We identified three trials[32,35,77] and four observational studies[127,150,158,159] that evaluated the impact of educational programs for clinicians on appropriate prescribing of antibiotics for acute RTIs and reported on changes in antibiotic prescriptions (Table 4, Evidence Table 5 [Appendix H]). All but one study used some form of localized education materials and two specifically studied prescribing for children. Two of the trials were poor quality and not assessed here.[32,77] The remaining studies were fair quality, with one trial focusing only on sinusitis in adults,[35] two observational studies of acute RTIs in children,[127,150] and one of both adults and children.[159] The fair-quality trials were cluster randomized. The studies did not attempt to evaluate appropriateness of prescribing (vs. not prescribing).

These studies provided low-strength evidence that clinician-based educational interventions are effective in reducing overall antibiotic prescribing for acute RTI, but the magnitude was modest and varied (range 1.4% to 10%). The effect varied depending on how the outcome was defined, the comparison intervention/group, the specific infection, and the study design and quality. For example, no effect was seen with a program focused only on adults with sinusitis.[35] This was the only trial in this group of studies, comparing an organized, expert-led discussion of a new guideline with usual care (similar groups left to discuss the guideline at their discretion), with the guideline itself mailed to all general practitioners in the area and a national campaign on rational use of antibiotics at the time of the study. The results indicated that the intervention produced an incremental increase in effect (1.4% difference). Two observational studies that targeted clinicians with known higher antibiotic prescribing rates at baseline found the largest impact (7% and 10% reductions).[127,158] Both studies of antibiotic use in children found a benefit of the intervention,[127,150] while studies in adults were mixed.[35,158] A fair-quality observational study found reduced prescribing for uncomplicated URTIs and AOM, but not pharyngitis.[150]

A fair-quality observational study assessing an intervention applied broadly across Ontario, Canada found a small initial drop in prescribing of antibiotics typically used in acute RTI that was maintained over a 2-year period of time.[159] This evidence is insufficient to draw conclusions about the sustainability of the intervention.

Outcomes by Subgroups

In further examining potential sources of heterogeneity we found that while all the observational studies found at least some significant differences, the one fair-quality trial found no effect. While this may suggest confounding in the observational evidence, the trial was small and may have been underpowered.

Table 4. Change in antibiotic prescribing after clinician education interventions (good- and fair-quality studies)

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
van Driel, 2007[35] N = 75 Adults with acute sinusitis Fair quality	cluster RCT November 2004 – March 2005	Intervention: Small group (quality circle) discussion of new local guideline. Control: Independently discuss guideline.	Intervention 56.9% vs. control 58.3% Adjusted OR 0.63 (95% CI, 0.29 to 1.37)
Vinnard, 2013[158] Provider N = 28 Patient N = 382 Adults with acute bronchitis, cough, pharyngitis, URTI Fair quality	Pre-Post February – August 2000, 2001 vs. February – August 2002, 2003	Intervention: Academic detailing for known high prescribers. Patients with prior acute RTI visit received mailings.) Control: No intervention.	Academic detailing: 43% vs. 33% (-10%); Compared with control adjusted Ratio of ORs 2.80 (95% CI, 1.32 to 5.95) Patient mailings: 18.9% vs. 14.2% (-4.7%); Compared with control adjusted Ratio of ORs 1.66 (95% CI, 0.73 to 3.80) Control: 57.8% vs. 58.6% (+0.8%)
Chowdhury, 2007[127] Practice N = 16 Children < 5 y; acute RTI Fair quality	Prospective observational study Dates unclear	Intervention: WHO acute RTI guidelines explained by a pediatrician one time; restricted to clinics with high baseline prescribing. Control: No intervention.	Intervention: 71% vs. 86% (-15%) Control: 89% vs. 81% (-8%) Difference between groups: -7% (p-values not reported; data not available to calculate)
Razon, 2005[150] N = 24 Children; acute RTI Fair quality	Pre-Post November – February 1999 – 2000 vs. 2000 – 2001	Intervention: 1-day seminar based on CDC principles given by pediatric infectious disease expert.	Pre vs. Post URTI: 13.8% vs. 11.5% (-2.3%); p<0.05 AOM: 93% vs. 87.4% (-5.6%); p<0.05 Pharyngitis: 83.7% vs. 83.4% (-0.3%); NS
Weiss, 2011[159] N = All Quebec Prescriptions for specific antibiotics Fair quality	January – December 2003 – 2004 vs. February 2005 – December 2007	Intervention: 2-page guidelines on prescribing for acute RTIs, urinary tract infections and *C. difficile*; support letters from key stakeholders	All antibiotics: -4.1 per 1000 population (95% CI, -6.6 to -1.6) in the first year after implementation Difference remained stable over following 2 years.

AOM = acute otitis media, CDC = Centers for Disease Control, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection

Combined Educational Interventions for Clinicians and Patients

We identified five fair-quality studies focused on acute RTI in children,[87,88,96,148,154] seven that focused on adults[56,97,100,133,141,142,57] and one fair-quality observational study that examined a public campaign that was not specific to adult or pediatric populations.[161] These studies evaluated the impact of combined educational programs targeted at both patients and clinicians on appropriate prescribing of antibiotics for acute RTIs, with six RCTs[56,87,88,96,97,100] (Table 5, Evidence Table 1 [Appendix D]) and five observational studies (Evidence Table 3 [Appendix F]).[133,141,142,148,154] one poor-quality trial [90] and one poor-quality observational study were not

considered further in the synthesis of the evidence (Evidence Tables 2 [Appendix E] and 4 [Appendix G]).[146]

The trials randomized or assigned clinician study groups by practitioner or clinic and the specific composition of clinician education varied somewhat across the studies, with most involving small group sessions led by a local expert, using national campaign materials or local or national guidelines on appropriate use of antibiotics in acute RTI (Table 5). Some were focused on specific infections (e.g., AOM), while others were comprehensive. Patient education most commonly took the form of educational pamphlets and waiting room posters reinforcing the key messages, with a few providing additional forms of education (e.g., an interactive computer program in waiting area).

Appropriate Prescribing

Two studies evaluated the appropriateness of prescribing for either sinusitis[133] or pharyngitis[96] using duration of symptoms as the only criterion (i.e., symptoms longer than 7 days for sinusitis and 9 days for pharyngitis). These two studies provided low-strength evidence of a significant benefit with uncertain magnitude, as one was measuring change in inappropriate prescribing and the other change in appropriate prescribing.[96,133] A fair quality trial of children with pharyngitis symptoms for less than 10 days found a combined education program to result in significant but moderate magnitude reduction in inappropriate prescribing (-10.4%; OR 0.62; 95% CI, 0.54 to 0.75).[96] An observational study found that the combination of an interactive computer patient education module and clinician education in an urgent care clinic resulted in a significant increase in the proportion of patients appropriately prescribed an antibiotic for acute sinusitis (+ 27%; 51% to 78%; $p<0.001$), with appropriateness defined as having symptoms for at least 7 days. No details were available about when counting began for duration of symptoms in either study.

A fair-quality trial in adults examined the effect of posters in waiting areas showing poster-sized "commitment letters" stating their clinicians' intention to improve appropriate antibiotic use and including information on appropriate antibiotic use and nonantibiotic treatments posted for 12 weeks starting in February.[57] Appropriateness of prescribing was determined based on a prespecified list of ICD-9 codes. Codes deemed to not require antibiotic treatment included acute nasopharyngitis, acute laryngopharyngitis, acute bronchitis, acute URTI, nonstreptococcal pharyngitis, and influenza. The method for determining which codes were appropriate and which were not was not described. Absolute percent change in inappropriate prescribing over 1 year after intervention (12 weeks) was -9.8 percent in the poster group and +9.9 percent in the control group (adjusted absolute difference -19.7%; 95% CI, -5.8 to -33.04). This study also analyzed the risk of shifting away from ICD-9 codes deemed inappropriate and for change in use of antibiotic-appropriate codes and found no statistically significant effect.

Overall Prescribing

The remainder of the studies (5 fair quality trials and 5 fair quality observational studies) provided moderate-strength evidence that combined clinician/patient educational interventions are effective in reducing overall antibiotic prescribing for acute RTI, with a modest magnitude of effect that varied depending on patient age, the specific infection targeted, statistical analysis, and the study design (e.g., comparison group). Across the RCTs, the mean reduction in overall antibiotic prescriptions was 7.3 percent (95% CI, 4.0 to 10.6) when intervention was compared with no intervention. Statistical pooling was not possible due to variation in data reporting.

Outcomes by Subgroups

Age. The impact of combined clinician and parent education programs on prescribing of antibiotics for acute RTI in children was inconsistent across two fair-quality cluster RCTs conducted by the same group of researchers when considering age of the child. The first was conducted in 12 practices in Massachusetts and while decreases were seen in both groups, overall antibiotic prescribing was reduced with the intervention.[88] In younger children (3 to <36 months), including only those present in both pre and post years and controlling for differences in prescribing at baseline, the intervention led to a reduction of 16 percent (95% CI, 8% to 23%). For older children, 36 to <72 months, the adjusted difference was 12 percent (2% to 21%). In the more recent study, 16 communities were cluster randomized to intervention or control.[87] This study also found significant decreases in overall use of antibiotics from baseline year to the end of followup at year 5 after adjustment for baseline prescribing, secular trends, gender and insurance type. However, in this community-based study, in children 3 to <24 months there was no additional decrease seen in the intervention group (-0.5%, p=0.69). For children 24 to <48 months (4.2%, p<0.01) and 48 to <72 months (6.7%, p< 0.001), small statistically significant decreases were seen. This study also found differences by type of insurance. Children covered by Medicaid had statistically significant reductions in prescribing across the 3 age groups (-4.5%, -5.5% and -9%, p≤ 0.01), while only the 48 to < 72 months groups had a significant reduction in children with commercial insurance (-5.1%, p<0.01).

An observational study evaluating a community-wide campaign aimed at reducing antibiotic prescribing in children found a reduction of 11 percent (95% CI, 8 to 14).[148] This study found the reduction greatest among children age 1 to 5 years, particularly among black children (18% reduction). A second observational study focused interventions on AOM, and found a 16 percent reduction (OR 0.25, 95% CI, 0.11 to 0.53) after intervention.[154]

Studies in adults showed some variation in findings based on the target infection and the intervention-control comparison. In a trial targeting adults presenting to EDs with acute RTI, patient and clinician education (compared with no intervention) led to reduced prescribing for uncomplicated URTI with a difference of 9 percent between groups, but not for acute bronchitis (difference <1%).[56] In contrast, the observational study of a patient interactive computer education module and clinician education described above found a large statistically significant reduction from baseline in overall antibiotic prescribing for acute bronchitis (-34%, p<0.001).[133] Antibiotic prescriptions for nonspecific URTIs were also reduced (-13%, p<0.001) while prescribing for pharyngitis or sinusitis did not change after the intervention. Similarly, in two related observational studies, combination patient and clinician education did not significantly reduce prescribing for pharyngitis (OR 0.53, 95% CI, 0.23 to 1.18) or rhinosinusitis (OR 0.65, 95% CI, 0.21 to 1.06).[141,142]

Two studies examined a potential dose-response effect in increasing the number or type of educational interventions. In a study of adults with acute RTI, continuous (monthly) education sessions reduced prescriptions by a smaller amount (3.5%) over annual seasonal education sessions than seen in the studies with no intervention as the control (mean 8.2%).[100] Intermediate reductions in prescribing of antibiotics was seen with the addition of clinician education specifically about acute cough in the setting of a national campaign aimed at educating patients about appropriate antibiotic use, difference of 6.5 percent.[97]

A study from Australia that incorporated public messaging and local clinician education about appropriate use of antibiotics for acute RTI in any age group, over a 4-year period, found little impact beyond pre-existing background efforts.[161] While the study reported modest but

significant decreases over the intervention period, it was not clear that there were important decreases related to the intervention. There was a preintervention decrease in prescriptions for antibiotics most commonly prescribed for acute RTIs of -3.5 per 1000 general practitioners per year and a postintervention decrease of -2.2 per 1000 general practitioners per year. While both are statistically significant ($p<0.0001$) compared with baseline, the difference between the rates was not significant ($p=0.1$). Community surveys indicated that in 1999, 10.8 percent of the community respondents had taken an antibiotic the last time they had a cough, cold, or flu. This number progressively decreased over the intervention years to a low of 7.4 percent in 2004 (change 3.4%).

Table 5. Change in antibiotic prescribing after patient and clinician education interventions

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Adults			
Meeker, 2014[57] Patient N = 954 Fair quality	RCT February – April 2012	Intervention: Waiting room posters of clinician letters of commitment to appropriate antibiotic use. Control: No intervention.	Inappropriate* Antibiotic Prescribing, % (95% CI): Intervention: 43.5% vs. 42.8% (-9.8%) Control: 33.7% vs. 52.7% (+9.9%) Adjusted difference in change poster vs. control: -19.7% (95% CI -5.8 to -33.04)
Chazan, 2007[100] N = 200 providers N = 168,644 patients Adults; RTIs Fair quality	RCT October 2000 – April 2003	Intervention: Monthly sessions; diagnostic tools; therapeutic recommendations. Control: Seasonal intervention (2 hour meeting + reminders for providers, educational leaflets for patients).	Total Antibiotic Use: Intervention vs. Baseline (daily dose/1000 patients/day): Seasonal Intervention group: 23.2 vs. 27.8 Continuous Intervention group: 22.9 vs. 28.7 (p for difference between groups <0.0001) Percent Decrease in Antibiotic Use: Continuous vs. Seasonal intervention: 20.0% vs. 16.5% (p<0.0001)
Coenen, 2004[97] N = 85 providers N = 1,503 patients Adults; acute cough Fair quality	Cluster RCT February – April 2000 and 2001	Intervention: National campaign + guideline on acute cough, academic detailing, and postal reminder. Control: National campaign.	Percent change in antibiotic prescribing: -15.6% vs. -9.1%; % difference -6.5% OR 0.56 (95% CI, 0.36 to 0.87)
Metlay, 2007[56] IMPACT Patient N = 5,500 Provider N = 16 Adults; acute RTI Fair quality	Cluster RCT November – February 2003 – 2004 vs. November – February 2004 – 2005	Intervention: *Clinicians*: Trained clinical leaders taught sessions and site-specific data. *Patients*: waiting/exam room posters and brochures and an interactive video kiosk in waiting rooms. Control: No intervention.	Antibiotic prescribed: Combined URTI or acute bronchitis: Intervention groups: 10% (95% CI, -18 to -2) Control groups: 0.5% (95% CI, -3 to +5) URTI:9.5% vs. -0.3% (no variance reported) Acute bronchitis:5.0% vs. -5.7% (no variance reported)

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Harris, 2003[133] N = 42 providers N = 1,518 patients Adults; acute RTI Fair quality	Prospective nonrandomized controlled trial October 2000 – April 2001	Intervention: (1) provider educational session based on CDC recommendations, (2) examination room posters, (3) Patient computer- based education. (Full intervention completed; limited intervention did not complete). Control: Baseline.	Antibiotic prescribed: Baseline vs. Limited Intervention vs. Full Intervention (%, p of Intervention vs. Baseline, p for limited vs. full): Bronchitis: 58 vs. 30 vs. 24, p< 0.001, NS Nonspecific URTI: 14 vs. 3 vs. 1, p< 0.001, NS Pharyngitis: 76 vs. 71 vs. 78, p=NS, NS Sinusitis < 7 days: 85 vs. 62 vs. 82, 0.06 (limited vs. baseline), p=NS Sinusitis ≥ 7 days*: 89 vs. 89 s. 97, p=NS, NS All ARI*: 45 vs. 31 vs. 35, p< 0.001, < 0.001
Llor, 2011[141] N = 339 providers N = 6,849 Adults; pharyngitis Fair quality	Pre/post study with post-intervention control group. First registry January/ February 2008, second registry January/ February 2009.	Intervention: prescriber training and clinical guidelines; patient handouts. Control: 2 other communities with no intervention. (2nd intervention group also received point-of-care testing, evaluated elsewhere in report)	Adjusted odds ratio; 95% CI for antibiotic prescriptions in intervention vs. control: OR=0.53; 95% CI, 0.23 to 1.2
Llor, 2012[142] N = 338 providers N = 5,385 patients Adults; LRTI Fair quality	Pre/post study with post-intervention control group. First registry winter of 2008, second registry winter of 2009.	Intervention: prescriber training and clinical guidelines; patient handouts. Control: 2 other communities with no intervention. (2nd intervention group also received point-of-care testing, evaluated elsewhere in report)	Adjusted odds ratio; 95% CI for antibiotic prescriptions of antibiotics in intervention versus vs. control groups: OR=0.42; 95% CI, 0.22 to 0.82
Children			
Cohen, 2000[a96] Patient N = 1,016 Parent N = NR Children ≤ 10 y; pharyngitis ≤ 9 days Fair quality	RCT Dates NR	Intervention: Educational material for parents and clinicians. Control: No intervention[b].	Change in number of inappropriate antibiotic prescriptions: 26.7% vs. 37.1% (-10.4%) OR 0.62 (95% CI, 0.54 to 0.75)
Finkelstein, 2001[a88] Patient N = 8,815 Provider N = 157 Children 3 to <72 mo. in 12 practices Fair quality	RCT December 1997 – November 1998	Intervention: *Clinicians*: Academic detailing by local trained peer leaders with CDC materials; 4-month reminder. *Parents*: CDC pamphlet; letter from pediatrician; waiting room posters/pamphlets. Control: No intervention.	Difference in antibiotics prescribed per-person year (per child, adjusted): 3 to <36 months: -7.1% (p<0.001) Analysis limited to patients in both baseline and followup data set: -16% (95% CI, 8 to 23) 36 to <72 months: -5.2% (p<0.001) Analysis limited to patients in both baseline and followup data set: 12% (95% CI, 2 to 21)

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Finkelstein, 2008[87] Patient N = 233,135 person-years Provider N = NR Children 3 to <72 mo. Fair quality	Cluster RCT October – March from 2000 – 2003	Intervention: *Clinicians*: Guideline dissemination, small-group education, prescribing audit/feedback, various items (e.g., prescription pads) with REACH Mass logo. *Patients* (parents): Brochure on appropriate antibiotic use, newsletters, interactive Web site, posters, etc. Control: No intervention.	Adjusted % change (over 3 years) 3 to <24 months: -20.7 vs. -21.2 (-0.5%; p=0.69) 24 to <48 months: -10.3 vs. -14.5 (-4.2%; p<0.01) 48 to <72 months: -2.5 vs. -9.3 (-6.7%; p<0.0001)
Perz, 2002[148] Provider N = 250 Patient N = 464,200 person-years Children; ARTI Fair quality	Time series 12-month periods before (May 1996 through April 1997), during (1997/98) and after (1998/99) intervention.	Intervention: Lectures for providers; prescribing guidelines; newsletters, pamphlets; patient education materials; media coverage and public service announcements. Control: 3 urban counties with no intervention.	Change in antibiotic prescription rates (% reduction; 95% CI): -11%; 95% Cl, -14 to -8 Ratio of antibiotic prescriptions to respiratory illness visits: White: -8% (-16 to 0) Black: -13% (-19 to 8)
Smabrekke, 2002[154] Practice N = 2 Patient N= 819 Children aged 1-15 y; AOM Fair quality	Controlled before/after. December 1997 to March 1998 (baseline); December 1998 to March 1999 (intervention)	Intervention: Symposium for providers. Pamphlets and oral education for parents. Control: Similar community with no intervention	Percent prescribed antibiotic (before vs after) Intervention: 90% (318/355) vs. 74% (155/209), p<0.01 Control: 95% (126/133) vs. 91% (114/125), p=0.5
Mixed Population			
Wutzke, 2007[161] Provider N = 5,758 Patient N = 12,217 Ages ≥ 15 y; URTI Fair quality	Before/after 1999 baseline, 2000 - 2004 intervention.	Intervention: Radio, television, and newspaper campaign. Implemented seasonally with community-based education sessions. Control: Precampaign.	Proportion of the community reporting taking antibiotics when ill with last cough, cold, or flu (% change, p) 1999 vs. 2000: 10.8 vs. 10.0 (- 0.8, NS) 1999 vs. 2001: 10.1 (- 0.7, NS) 1999 vs. 2003: 9.8 (- 1.0, NS) 1999 vs. 2004: 7.4 (-3.4, p< 0.05)

*Codes deemed to not require antibiotic treatment included acute nasopharyngitis, acute laryngopharyngitis, acute bronchitis, acute URTI, nonstreptococcal pharyngitis, and influenza.

[a] Included in published systematic review[16]; [b] abstract in English, primary study in French – included in published systematic review[16]

AOM = acute otitis media, ARI = acute respiratory infection, CDC = Centers for Disease Control, ECS = Emergency Call Service, GP = general practitioner, LRTI = lower respiratory tract infection, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection.

Communication Strategies

Strategies to Improve Clinician-Patient Communication Compared with Usual Care

We identified five fair quality RCTs that compared interventions to improve clinician-patient communication with usual care and met inclusion criteria.[67,75,76,105,119,120] (a sixth study was excluded for poor quality[119]). These trials studied different interventions to improve communication between clinicians and patients regarding the use of antibiotics for acute RTIs and reported on changes in antibiotic prescriptions (Table 6, Evidence Table 1 [Appendix D]). In fair-quality trials, the interventions targeted clinicians only in four trials[67,75,76,105] and patients

only in one trial.[120] Two trials studied interventions specifically designed to improve shared decisionmaking, an approach in which the values, preferences, and opinions of both the patient and the clinician are made explicit and considered in the decision.[75,76] The second of these shared decisionmaking trials[76] studied a revised version of the intervention used in the first trial.[75] Two trials[67,105] were factorial designs aimed at clinicians that assessed two interventions – one to enhance communication skills and one to train clinicians in the use of point-of-care CRP testing, and another trial was a factorial design study aimed at patients only.[120] All of the clinician-based studies were cluster randomized, while the patient-based trial was not. All but one of the five clinician interventions involved some form of in person training by study personnel; one clinician intervention was mostly internet-based[67] and two others included some video or internet-based training.[75,76]

Five fair-quality studies evaluated the indirect outcome of *overall* prescription of antibiotics for acute RTIs.[67,75,76,105,120] These five studies consistently found communication interventions to reduce the relative risk of antibiotic prescription for acute RTIs compared with usual care (range from 0.17 to 0.69; Table 6), with findings statistically significant in all but one study.[75] Absolute risk reductions ranged from 9.2 to 26.1 percent. The heterogeneity of the various strategies and approaches to improving clinician-patient communication precluded a pooled analysis.

Outcomes by Subgroups

Although few studies conducted subgroup analyses, the general finding of an overall reduction in antibiotic prescribing was seen across studies that varied in the types of RTI included, signs and symptoms reported, age of patients (adult and child), and geographic region. All but one study was conducted during the winter and spring months, with no comparisons of effectiveness by time of year. A large study (clinician n=372; patient n=4264) reported on differences in overall prescribing according to LRTI versus URTI.[67] This study – which was predominantly aimed at patients with LRTIs (80%), but included patients with URTI (20%) – found the communication intervention to be associated with slightly lower relative risk of antibiotic prescribing for LRTIs (RR 0.67; 95% CI, 0.46 to 0.88) than for URTIs (RR 0.78; 95% CI, 0.43 to 1.21), but with overlapping confidence intervals. No other studies reported any subgroup analyses of possible differences in effectiveness according to factors such as patient characteristics, clinician characteristics, target of the interventions, diagnostic methods used, or other contextual factors.

While reductions were seen in all five studies, the reduction was greatest in the one study with an intervention aimed at patients only; a small fair-quality, factorial design trial that found a reduction in antibiotic prescribing of OR 0.17 (95% CI, 0.03 to 0.93) compared with a usual care control group.[120]

Strategies to Improve Clinician-Patient Communication Compared with Point of Care C-reactive protein Testing (head to head comparisons)

Two fair-quality trials compared strategies to improve clinician-patient communication with point-of-care CRP testing (Table 6, Evidence Table 1).[67,105] Both trials evaluated overall antibiotic prescribing, not appropriate prescribing specifically. Each used a different communication training intervention targeting clinicians. One trial (N=258), based on motivational interviewing, used in person training and simulated patients[105] and found no difference between communication training and CRP testing in reducing overall antibiotic prescribing for acute RTIs (RR 0.85; 95% CI, 0.58 to 1.25). The other trial (N=4264) used a

Web-based training program with illustrative video clips[67] and found communication training to be associated with a modestly higher relative risk of overall antibiotic prescription compared with CRP testing (RR 1.17; 95% CI, 1.05 to 1.31).

Outcomes by Subgroups

Diagnosis. One of the trials reported on differences in overall prescribing according to URTI versus LRTI.[67] This study found no difference in the degree of reduction of antibiotic prescribing for communication training compared with CRP testing in patients with URTIs (28.3% vs. 27.4%; unadjusted RR 1.04; 95% CI, 0.76 to 1.41) and modestly smaller reduction in patients with LRTIs (43.5% vs. 36.4%; unadjusted RR 1.20; 95% CI, 1.07 to 1.34), but with overlapping confidence intervals. Neither study reported any subgroup analyses of possible differences in effectiveness according to factors such as patient characteristics, clinician characteristics, target of the interventions, diagnostic methods used, or other contextual factors.

Age. The magnitude of effect was larger in the single study of antibiotic prescribing in children compared with the studies in adults.

Table 6. Interventions to improve communication between clinicians and patients

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Children			
Alder, 2005[120] Practice N = 2 Provider N = NR Patient N = 80 Parents of child patients (1 to 10 y); acute ear pain, sore throat, cough, congestion and/or fever Fair quality	2 X 2 factorial RCT (patient level). August 2000 – December 2000 Followup: None	Intervention: *Communication*: Given four questions to ask clinician; role-playing exercises; breathing technique. *Education*: Information-only on antibiotic use. *Combination*: Communication + Education. Control: Information on general child nutrition.	Antibiotics prescribed at index visit: Communication vs. Control: OR (95% CI): 0.17 (0.03 to 0.93)
Adults			
Cals, 2009[105] Practice N = 20 Provider N = 40 Patient N = 431 Adults; suspected LRTI, cough < 4 weeks Fair quality	2 X 2 factorial cluster RCT (clinic level). September 2005 – March 2006 and September 2006 – March 2007. Followup: 28 days for most patients (maximum 10 weeks).	Intervention: *Communication skills training*: based on 11 key tasks (e.g., exploring patient's fears and expectations, asking patient's opinion of antibiotics), and elicit-provide-elicit framework. Control: Usual Care	Antibiotics prescribed at index visit: Communication vs. Control: 33.3% vs. 66.7%; unadjusted RR 0.50 (95% CI, 0.36 to 0.69) Communication vs. CRP: 33.3% vs. 39.1%; unadjusted RR 0.85 (95% CI, 0.58 to 1.25)

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Little, 2013[67] Practice N = 228 Provider N = 372 Patient N = 4,264 Patients (> 18 y); acute RTI (upper or lower) Fair quality	2 X 2 factorial cluster RCT (clinic level). February 2011 – May 2011. Followup: 4 weeks	Intervention: *Communication skills training*: Internet-based training in communication skills; interactive booklet; video demonstrations. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual care.	Antibiotic use at index consultation (reported by clinicians): Communication + Combination vs. CRP + Control: 36% vs. 45%; adjusted* RR 0.69 (95% CI, 0.54 to 0.87) Communication vs. Control: 41% vs. 58%; unadjusted RR 0.68 (95% CI, 0.50 to 0.89) Communication vs. CRP: 41% vs. 35%; unadjusted RR 1.17 (95% CI, 1.05 to 1.31) Communication vs. Control: URTI: adjusted* RR 0.82 (95% CI, 0.53 to 1.18) LRTI: adjusted* RR 0.66 (95% CI, 0.51 to 0.84)
Mixed (adults and children)			
Légaré, 2010[75] Practice N = 4 Provider N = 33 Patient N = 459 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2007 – March 2008 Followup: 2 weeks	Intervention: Interactive workshops on URTIs, risk communication, fostering patient participation in decisionmaking, shared decisionmaking support tools. Control: Delayed intervention.	Used antibiotics immediately after consultation: Baseline: 56% vs. 54% After experimental group received intervention (Time 1): 33% vs. 49% After control group received intervention (Time 2): 35% vs. 46% Difference at Time 1 (95% CI): -16 (-31 to 1), p=0.08. Proportion who filled prescription: Baseline: 79% vs. 70% Time 1: 45% vs. 51% Difference at Time 1 (95% CI): -6 (-17 to 6), p=0.35.
Légaré, 2012[76] Practice N = 9 Provider N = 149 Patient N = 359 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2010 – April 2011 Followup: 2 weeks	Intervention: 2-hour online tutorial and 2-hour onsite interactive workshop on decisionmaking about antibiotic treatment for RTIs and communication with patients. Control: Usual care.	Antibiotic use immediately after consultation: Baseline: 41.2% vs. 39.2% After intervention: 27.2% vs. 52.2% Absolute difference: 25.0% Adjusted RR (95% CI): 0.5 (0.3-0.7)

* Adjusted for multiple factors, including clustering by physician and practice.
CRP = C-reactive protein, LRTI = lower respiratory tract infection, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection

Clinical Interventions

Delayed Prescribing Strategies

We primarily relied on findings from a good-quality Cochrane review for evaluating the comparison of delayed prescribing strategies to immediate or no prescribing.[14] The Cochrane review included seven RCTs that reported antibiotic use outcomes.[41,66,68,72,91,101,117] The trials addressed comparisons of delayed versus immediate antibiotic prescriptions[41,66,68,72,91,117] and delayed versus no antibiotic prescriptions.[66,68,101] We included two additional trials that compared different methods of delaying prescriptions, including giving prescriptions with instructions, leaving prescriptions for collection, postdating prescriptions, or requesting

recontact[30,70] and one trial that compared delayed prescribing to use of a clinical prediction score.[71]

Delayed versus immediate. There was low-strength evidence that delayed antibiotics result in significantly reduced antibiotic use compared with immediate antibiotics. Compared with immediate prescribing, odds of reduced antibiotic use were greatest when the delayed prescription was kept at reception to be picked up if needed (range of absolute differences: -63% to -76%; range of OR's [95% CI]: 0.00 [0.00-0.02] to 0.05 [0.02-0.08])[66,68,72,91] compared with when the delayed prescription was issued to the patients with instructions to delay (range of absolute differences: -34% to -49% OR 0.09; 95% CI, 0.05 to 0.17 to 38% vs. 87%; OR 0.20; 95% CI, 0.09 to 0.44).[41,117] The Cochrane review did not present results of their pooled analyses because of significant heterogeneity, which may have been due to the clinical diversity of participants that included adults and children with common cold, cough and sore throat, and AOM.

Antibiotic use rates ranged from 33 to 44 percent for different methods of delaying prescriptions.[30,70]

Delayed versus delayed. Compared with issuing a prescription with instructions to delay, there was low-strength evidence that alternative delaying strategies do not lead to further reductions in antibiotic use, including postdating the prescriptions (OR 1.05; 95% CI, 0.68 to 1.62), leaving prescriptions for collection (OR 1.32; 95% CI, 0.68 to 2.58), or requesting recontact (OR 1.11; 95% CI, 0.58 to 2.11).

Delayed versus clinical prediction score. There was low-strength evidence from the fair-quality PRISM RCT (primary care streptococcal management) that use of the FeverPAIN clinical score (immediate antibiotics for score ≥4, delayed antibiotics for scores of 2-3, and no antibiotics for scores of 0-1) statistically significantly reduced overall antibiotic use compared with using a delayed prescription strategy of leaving the prescription for collection after 3-5 days (37% vs. 46%; RR 0.71; 95% CI, 0.50 to 0.95).[71]

Outcomes by Subgroups

Although there was variation across studies in antibiotic use, it was difficult to determine whether it is due to any particular subgroup characteristic of interest as studies differed on multiple factors, including type of RTI, type of delay strategy, type of clinic, geographic region, and time period. For example, the study with the greatest reduction in overall antibiotic use (OR 0.00; 95% CI, 0.00 to 0.07) involved patients with cough who were seen in general practitioners offices in Scotland between December 1997 and November 1998 who were required to wait a week before returning for their delayed prescription.[91] In contrast, the study with the smallest reduction in overall antibiotic use (OR 0.20; 95% CI, 0.09 to 0.44) involved patients with the common cold who were seen in family practice clinics during an unspecified time period who were given the delayed prescription at the time of the visit and only instructed to wait 72 hours.[117]

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

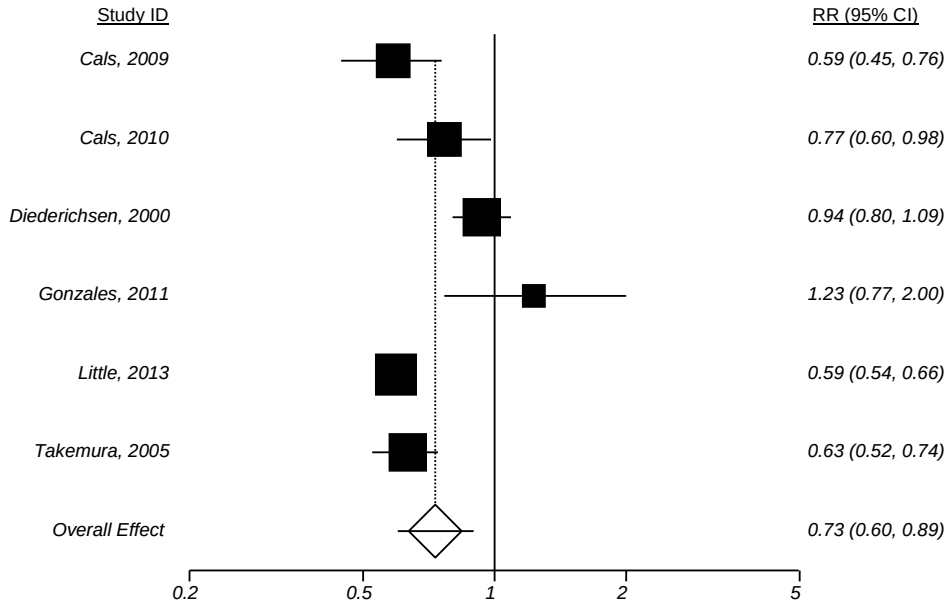
C-Reactive Protein Testing Compared with Usual Care

Five RCTs[40,67,93,103,105] and one observational study[123] compared CRP testing for acute RTI with usual care and met inclusion criteria (Table 7, Evidence Tables 1 [Appendix D] and 3

[Appendix F]). All six studies were fair quality and were conducted in primary care practices. Five of the six studies were conducted in Europe and one trial[40] was conducted in Japan. In each study, CRP testing was done at the time of the clinic visit. The studies varied in the type and amount of guidance provided to clinicians for interpreting CRP test results and making antibiotic prescription decisions. Three trials used guidelines with three or four defined levels of CRP and suggested or stated that 100 mg/L is a threshold at which antibiotics would likely be indicated.[67,103,105] One trial provided no explicit guidance, but indicated that CRP <10 mg/L is normal and that CRP <50 mg/L is seldom due to bacterial infection.[93] Another trial did not describe any clinical guidance and indicated that physicians used a "reference level" of CRP ≤5 mg/L.[40] In the single observational study, CRP levels were reported to clinicians in five categories ranging from 0-9 mg/L to >100 mg/L, but no explicit prescribing guidance was provided.[123] Two of the studies were clinic cluster-randomized 2 X 2 factorial trials of CRP testing and an intervention to improve communication between clinicians and patients.[67,105] The remaining three trials were each randomized at the level of the patients.[40,93,103] One trial used CRP testing only in conjunction with white blood cell (WBC) measurement.[40]

In a pooled analysis of five RCTs (Figure 3), CRP testing was associated with lower antibiotic prescribing or use compared with usual care (RR 0.69; 95% CI, 0.57 to 0.84).[40,67,93,103,105] In stratified analysis, the relative risk of antibiotic use was slightly lower for cluster-RCTs (two trials; RR 0.59; 95% CI, 0.54 to 0.65; I^2=0.0%) compared with those that randomized at the patient level (three trials; RR 0.77; 95% CI, 0.59 to 1.00; I^2=82.9%) with no significant heterogeneity in the cluster-RCT group but with overlapping confidence intervals. In a sensitivity analysis excluding the relatively small trial that used CRP in conjunction with WBC testing,[40] the pooled relative risk was essentially unchanged (four trials; RR 0.71; 95% CI, 0.55 to 0.92; I^2=88.4%). The single observational study found that general practitioners with access to CRP tests prescribed antibiotics for acute sinusitis less frequently than those without access to CRP tests (59% vs. 78%; OR 0.43; 95% CI, 0.33 to 0.58).[123] While the strength of evidence regarding the effectiveness of CRP testing in reducing *overall* antibiotic prescribing would be moderate, the indirectness of the measure limits the strength of evidence to a grade of low for *appropriate* prescribing (Table 7).

Figure 3. Overall antibiotic prescribing with C-reactive protein testing compared with usual care



Outcomes by Subgroups

Although few studies conducted subgroup analyses, the general finding of an overall reduction in antibiotic prescribing was seen across studies that varied in the types of RTI included, signs and symptoms reported, age of patients (adult and child), and country. All studies were conducted during the winter months and some also included spring and autumn months, with no comparisons of effectiveness by time of year.

Diagnosis. Three studies reported on differences in prescribing according to the anatomical site of the RTI. A large trial (clinician n = 372; patient n = 4264) found no difference in the effectiveness of CRP testing (compared with no CRP testing) when used in patients with URTI compared with those with LRTI. For patients with URTIs, the adjusted relative risk (95% CI) of antibiotic prescribing was 0.50 (0.31 to 0.79), and for those with LRTIs it was 0.53 (0.39 to 0.68), with overlapping confidence intervals.[67] Another trial (clinician n = 33; patient n = 258) found no difference in the effectiveness of CRP testing in rhino compared with LRTIs, with unadjusted relative risks of 0.75 vs. 0.81, respectively, and overlapping 95% confidence intervals of (0.55 to 1.02) and (0.53 to 1.03).[103] A third trial reported no difference in antibiotic prescribing between the CRP testing group and the usual care group according to anatomic location of RTI (middle ear, sinus, chest, other), with results presented diagrammatically as overlapping confidence intervals but with no statistical test results.[93]

CRP Testing Compared with Other Strategies (Head-to-Head Comparisons)

Two fair-quality trials compared CRP testing with strategies to improve communication regarding the use of antibiotics for acute RTIs between clinicians and patients, coming to different conclusions (Table 7, Evidence Table 1 [Appendix D]).[67,105] These studies are described in detail in the section on strategies to improve communication between clinicians and patients (above). Each of the trials used a different communication training intervention targeting clinicians, one finding no difference between CRP testing and communication training in reducing overall antibiotic prescribing for acute RTIs (RR 1.17; 95% CI, 0.80 to 1.72)[105] and the

other finding the use of CRP testing to modestly reduce the overall antibiotic prescribing for acute RTIs (RR 0.85; 95% CI, 0.77 to 0.95).[67] This evidence is insufficient to draw conclusions.

One fair-quality study compared the effectiveness of a clinical algorithm with and without point-of-care CRP testing as part of the algorithm.[81] The algorithm was used in an urban ED to guide chest x-ray and antibiotic treatment decisions for acute cough illness. Low-strength evidence from this study suggested no statistically significant difference in antibiotic prescribing when CRP testing was included as part of the algorithm compared with use of the clinical algorithm alone (37% vs. 31%; RR 1.23; 95% CI, 0.77 to 2.00). This evidence is insufficient to draw conclusions (Appendix J).

Outcomes by Subgroups

Diagnosis. The larger trial reported no difference in the degree of reduction of antibiotic prescribing with CRP testing compared with communication training in patients with URTIs (27.4% vs. 28.3%; unadjusted RR 0.97; 95% CI, 0.71 to 1.32) and a modestly greater reduction in patients with LRTIs (36.4% vs. 43.5%).[67]

Table 7. C-reactive protein point-of-care testing interventions

Study and Characteristics	Study Details	Intervention and Control Details	Outcomes
RCTs			
Cals, 2009[105] Practice N = 20 Provider N = 40 Patient N = 431 Adults; suspected LRTI, cough < 4 weeks Fair quality	2 X 2 factorial cluster trial. September 2005 - March 2006 and September 2006 - March 2007. Followup: 28 days for most patients (maximum 10 weeks).	Intervention: *CRP testing*: testing during consultation, with guidance on interpretation. *Communication skills training*: based on 11 key tasks (e.g., exploring patient's fears and expectations, asking patient's opinion of antibiotics), and elicit-provide-elicit framework. *Combination*: CRP + Communication. Control: usual care.	Antibiotics prescribed at index visit: CRP + Combination vs. Communication + Control: 30.8% vs. 52.9%, p=0.02 (adjusted model); CRP vs. Control: 39.1% vs. 66.7%; CRP vs. Communication: 39.1% vs. 33.3%; Antibiotic within 28-days of index visit: CRP + Combination vs. Communication + Control: 44.9% vs. 58.3%, p<0.01 (adjusted model)
Little, 2013[67] Practice N = 228 Provider N = 372 Patient N = 4,264 Patients (>18 y); acute RTI (upper or lower) Fair quality	2 X 2 factorial cluster trial. February 2011 – May 2011. Followup: 4 weeks.	Intervention: *CRP testing*: testing during consultation, with guidance on interpretation and prescribing. *Communication skills training*: internet-based training in communication skills; interactive booklet consultations; video demonstrations. *Combination*: CRP + Communication. Control: usual care.	Antibiotic use at index consultation (reported by clinicians): CRP + Combination vs. Communication + Control: 33% vs. 48%; adjusted*** RR 0.54 (95% CI, 0.42 to 0.69) CRP vs. Control: 35% vs. 58%; unadjusted RR 0.59 (95% CI, 0.54 to 0.66) CRP vs. Communication: 35% vs. 41%; unadjusted RR 0.85 (95% CI, 0.77 to 0.95) URTI: adjusted*** RR 0.50 (95% CI, 0.31 to 0.79) LRTI: adjusted*** RR 0.53 (95% CI, 0.39 to 0.68)

Study and Characteristics	Study Details	Intervention and Control Details	Outcomes
Cals, 2010[103] Practice N = 11 Provider N = 33 Patient N = 258 Adults (≥ 18 y); first consultation for LRTI or rhino Fair quality	November 2007- April 2008. Followup: 28 days.	Intervention: CRP testing during consultation. Clinicians advised to combine CRP results with clinical findings. Control: usual care (immediate, delayed, or no antibiotics).	Antibiotic use after index visit (used immediately or filled a delayed prescription): Overall: 43.4% vs. 56.6%; adjusted* RR 0.77 (95% CI, 0.56 to 0.98). Rhino: 45.2% vs. 60.3%; unadjusted RR 0.75 (95% CI, 0.55 to 1.02). LRTI: 41.1% vs. 51.0% unadjusted RR 0.81 (95% CI, 0.53 to 1.03). Antibiotic within 28-days of index visit: Overall: 52.7% vs. 65.1%; adjusted* RR 0.81 (95% CI, 0.62 to 0.99). Rhinosinusitis: 57.5% vs. 69.2% unadjusted RR 0.83 (95% CI, 0.65 to 1.06). LRTI: 46.4% vs. 58.8% unadjusted RR 0.79 (95% CI, 0.55 to 1.14).
Diederichsen, 2000[93] Practice N = 35 Provider N = 35 Patient N = 812 Adults, children; RTI Fair quality	January 1997- April 1997. Followup: 7 days.	Intervention: CRP testing during consultation. No strict guidelines for use of antibiotics. Control: usual care (clinical assessment only).	Frequency of antibiotic prescription: 43% (95% CI, 40% to 47%) vs. 46% (95% CI, 43% to 50%); adjusted** OR 0.9 (95% CI, 0.70 to 1.20)
Gonzales, 2011[81] Practice N = 1 Provider N = NR Patients N = 131 Adults (≥18 y); cough ≤21 days and one other acute RTI symptom Fair quality	November 2005 – March 2006. Followup: 2 to 4 weeks.	Interventions: *CRP testing + algorithm:* CRP testing and clinical management algorithm to guide chest x-ray and antibiotic treatment decisions. *Algorithm only:* Clinical management algorithm (without CRP testing) to guide chest x-ray and antibiotic treatment decisions.	Antibiotic treatment at index visit: CRP + Algorithm vs. Algorithm only: 37% (95% CI, 26% to 48%) vs. 31% (95% CI, 19% to 43%); unadjusted RR 1.23 (95% CI, 0.77 to 2.00).
Takemura, 2005[40] Practice N = 1 Provider N = 11 Patients N = 301 Patients with fever (≥ 37.5° C) and suspected infection Fair quality	December 2000 – January 2003. Followup duration not reported.	Intervention: CRP + WBC testing at time of consultation. Clinical guidance not described; CRP reference level ≤ 5 mg/L. Control: usual care.	Antibiotics received: 57.5% vs. 91.0%; unadjusted RR 0.63 (95% CI, 0.52 to 0.74)
Observational			
Bjerrum, 2004[123] Practice N = 367 Provider N = 367 Patient N = 1,444 Patients with acute sinusitis; median age, y (IQR)=40/41 (31 – 54) Fair quality	Observational November 2001 – January 2002. Followup: None.	Intervention: access to CRP testing. Control: no access to CRP testing.	Antibiotics prescribed: 59% vs. 78%; adjusted**** O 0.43 (95% CI, 0.33 to 0.58)

* Adjusted for clustering; ** Adjusted for age, clinical findings, and symptom duration; ***Adjusted for multiple factors, including clustering by physician and practice; ****Adjusted for patient sex, patient age, number of patients listed in practice, and clinician workload.

CAP, community acquired pneumonia, CRP = C-reactive protein, ED = emergency department, LRTI = lower respiratory tract infection, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection, WBC = white blood cell

Procalcitonin Point-of-Care Testing

Adults

We found a good quality systematic review (in 2 publications) on the use of procalcitonin in assisting with diagnosis and treatment decisions for adults with a range of RTIs (Table 8).[162,163] Although the review included diagnoses that are not included here (e.g. community acquired pneumonia), and was primarily aimed at determining the value of procalcitonin by setting (primary care, ED, intensive care unit), subgroup analyses provide information relevant to this review on overall antibiotic prescribing (appropriate prescribing was not measured). In the review, two trials (one good- and one fair-quality) in the primary care setting assessed the use of procalcitonin in adults with upper or lower acute RTI.[107,109] Both used algorithms that suggested antibiotics were not necessary with procalcitonin levels <0.25 mcg/L, one study evaluated a single measurement at diagnosis,[107] and the other included a repeat measure 6-24 hours later in patients not given antibiotics.[109] The review finds that use of a procalcitonin algorithm for prescribing in the primary care setting led to fewer antibiotics being prescribed compared with no procalcitonin results (OR 0.1; 95% CI, 0.07 to 0.14). The risk difference between the groups was 74 percent in one trial and 42 percent in the other. The trial with the largest difference in prescribing had a high incidence of antibiotic prescribing in the control group (97%). Nineteen percent of these patients had been diagnosed with a nonacute RTI infection such as CAP.[109] The other study had a lower prescribing rate in the control group, 36.7 percent, with 8 percent of patients having nonacute RTI diagnoses.[107] Both studies were conducted in European countries; therefore, applicability to the US setting is unclear. These studies provide moderate strength evidence on overall antibiotic prescribing.

The review also conducted subgroup analyses of data from four trials (2 good, 2 fair) [44,98,107,109] to examine rates of prescribing for URTI and acute bronchitis separately, and found that both were reduced with the use of procalcitonin. The pooled the absolute difference in prescribing was 33%for URTI (OR 0.14; 95% CI, 0.09 to 0.22 and 0.15) and 42% for bronchitis (95% CI, 0.10 to 0.23).[44,98,107,109]

Children

A single good-quality RCT of procalcitonin use in pediatric patients included children ages 1 to 18 presenting to two EDs in Switzerland with LRTIs, an adult procalcitonin algorithm was applied in one group and not the other (randomization at the patient level).[116] The study reports overall antibiotic prescribing. All patients also had CRP measurements taken and procalcitonin was measured again at day 3 and 5. Of children with a LRTI diagnosis other than CAP (36% of those enrolled), the difference in prescribing of antibiotics on day one was 21.7 percent more antibiotic prescribing in the procalcitonin group than the control group (RR 4.34; 95% CI, 2.40 to 7.84; calculated for this report). This was low-strength evidence of greater overall antibiotic prescribing with use of procalcitonin as a point-of-care test in children.

Outcomes by Subgroups

Diagnostic certainty. The use of a procalcitonin algorithm can be considered a method to improve the clinician's diagnostic certainty, or a measure of the clinician's perception of the patient's illness severity. The algorithms used in these studies were consistent in that a level of ≤25 mcg/L was considered to indicate that antibiotics were unlikely to be necessary, such that there was no variation in the use of this cutoff for "appropriate" use of antibiotics across the studies to be evaluated, even if this is an indirect measure of appropriateness. Examination of

specific decisions made by clinicians that deviated from the algorithm may have shed light on these questions. All four studies in adults reported greater than 70 percent compliance with the algorithm, and any impact of deviations from the algorithm based on clinician perception of individual patient illness severity couldn't be determined from these studies.

Age. The evidence currently available is distinctly different for adults and children. Procalcitonin was very effective in improving antibiotic use in adults with both upper and lower acute RTI, while there was an opposite effect in children. Although this finding is limited to a single study,[116] it was a good-quality study with adequate sample size to detect a difference of 15 percent between groups with a LRTI diagnosis other than CAP. In the adult studies, an effect was seen in primary care, as well as in subgroups based on diagnosis of URTI and acute bronchitis.

Table 8. Studies of procalcitonin testing on appropriate antibiotic prescribing and/or use

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Children			
Baer, 2013[116] Patient N = 337 Provider N = NR Practice N = 2 Children and adolescents, 1 mo. – 18 y Good quality	RCT January 2009 – February 2010	Intervention: procalcitonin-guided antibiotic treatment (initiation, continuation, or termination of antibiotic treatment strictly guided by procalcitonin cut-off levels). Control: clinically-guided standard care.	Antibiotic prescription within 14 days of randomization: N (%): 27 (45) vs. 10 (17) Rate difference (95% CI): 28 (12 to 43) OR (95% CI): 4.09 (1.80 to 9.93)
Adults			
Schuetz, 2011[163] Schuetz, 2012[162] Good quality	Systematic Review RCT dates: range 2002 - 2008	Intervention: procalcitonin-guided approach to antibiotic therapy in patients with respiratory infections. Includes non-acute RTIs, with subgroup information on acute RTIs. Organized by setting. PCT level of ≤25 mcg/L interpreted as not requiring antibiotics. Control: standard approach to antibiotic therapy.	Initiation of antibiotics, PCT vs. Control Adjusted OR; 95% CI ARTI in Primary Care Setting: OR= 0.1; 95% CI, 0.07 to 0.14 Upper ARI: OR=0.14; 95% CI, 0.09 to 0.22 Acute bronchitis: OR=0.15; 95% CI, 0.10 to 0.23

LRTI = lower respiratory tract infection, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection

Viral Point-of-Care Testing

A good-quality systematic review, five fair quality RCTs, and one fair-quality observational study evaluated the utility of rapid viral testing in reducing overall antibiotic prescribing for acute RTI in adults, children, or a mixed population.[52,78,108,112,125,164,166] There was one additional study rated poor quality.[54] Low strength evidence suggests a beneficial effect of multi-viral point-of-care testing in reducing overall antibiotic use in adults, but that use of rapid influenza testing in children does not affect overall antibiotic use. Evidence on the use of rapid influenza testing on overall antibiotic use in a mixed age population, with more adults than children, was insufficient.

Adults

A fair-quality RCT of using a multi-viral reverse transcriptase polymerase chain reaction (PCR) point-of-care test with results being either available within 24 hours or in delayed fashion

(8 or more days later) in adult patients with acute RTI found the proportion of patients prescribed antibiotics within 48 hours of initial visit was significantly lower in the patients assigned to point-of-care testing; 4.5 versus 12.3 percent (7.8% difference; p<0.01). [108] This test included 13 respiratory viruses (parainfluenza virus types 1 through 3, influenza viruses A and B, human metapneumovirus, respiratory syncytial virus, human rhinovirus, enterovirus, adenovirus, and human coronavirus types 229E, OC43, and NL63) and Mycoplasma pneumoniae and Chlamydophila pneumoniae. This evidence is low strength.

Children

In contrast, a good quality systematic review[164] of four trials[52,78,112,166] of point-of-care testing specifically for influenza in children in the ED setting found no benefit in reducing overall antibiotic prescribing. The review reports that together, the four studies included a total of 759 children in viral point-of-care testing arms and 829 patients in comparator groups. Rates of antibiotic use varied between 18 and 32 percent in viral point-of-care testing arms and 21 to 30 percent in comparator groups. While one reported a significant difference in the proportion of patients given antibiotics between physicians using point-of-care test results versus those in comparator arms (RR 0.66; 95% CI, 0.45 to 0.96), the pooled estimate reported showed a mild and nonsignificant decrease in total antibiotic use in the ED (RR 0.89; 95% CI, 0.71 to 1.12). This evidence is low strength.

Mixed Populations

A retrospective observational study conducted using ED data on rapid influenza testing from the National Hospital Ambulatory Medical Care Survey evaluated three influenza seasons from 2007 to 2009 and included all age groups, with one-third being children ages 0-5 years. [125] In this study, rapid influenza testing resulted in fewer antibiotic prescriptions after diagnosis of influenza compared with no testing and a diagnosis of influenza (11% vs. 23%; p=0.05). It is important to note that this analysis is limited to those diagnosed with influenza but without chart review true appropriateness of antibiotic prescribing cannot be determined. The authors note that the number of patients in1896) the referent group (test positive and diagnosis positive was very small, N=30). This evidence is insufficient to draw conclusions.

S. pneumococcal Point-of-Care Testing (Rapid Strep Tests)

Three fair-quality RCTs evaluated the utility of point-of-care testing using rapid strep tests compared with usual care or a clinical score.[31,61,65] All were conducted in the outpatient setting among primary care physicians (general practitioners, family practitioners, pediatricians); eligible patients had acute pharyngitis symptoms and one enrolled children, one enrolled both adults and older children, and one restricted to adults. Only one measured appropriateness of antibiotic use, determined by throat culture; appropriate prescribing were cases with positive culture with antibiotics prescribed negative culture without antibiotics prescribed.[65] Two studies reported similar sensitivity (89.8% and 83.1%) and specificity (93.8% and 93.3%) for the tests.[61,65]

All three trials found that the rapid strep test decreased overall antibiotic prescribing for acute pharyngitis by 20 to 52 percent (Table 9). In the one study directly measuring appropriate antibiotic use, the authors used a clinical score to determine “appropriateness.” The proportion of patients appropriately prescribed antibiotics in the rapid strep test arm versus the standard care was 22.9 versus 6.0 percent, a statistically significant decrease of 16.9 percent.[65]

Outcomes by Subgroups

Location. One of the trials stratified the randomization of physician groups by practice location and found that the rapid strep test resulted in a much steeper drop in prescriptions among hospital-based clinicians compared to clinicians in private practice.[61]

Age. None of the studies suggested differential effectiveness based on age of the patient.

Table 9. Randomized controlled trials evaluating the utility of point-of-care rapid strep testing compared with usual care or clinical score

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Maltezou, 2008[61] Greece Patient N = 820 Provider N = 24 Children (2-14 y); pharyngitis Fair quality	Group RCT December 2005 – June 2006 and September 2006 – June 2007	Intervention: 1) Private practice pediatricians Rapid strep test and culture. 2) Hospital-affiliated pediatricians Rapid strep test and culture. Control: Private practice pediatricians' usual care.	Control vs. Intervention in private practice and vs. hospital-based % Antibiotic prescribed: 72.2% vs. 33.7% vs. 19.8%, p=0.004
Worrall, 2007[31] Newfoundland Patient N = 533 Provider N = 40 Adults; acute sore throat Fair quality	Cluster RCT February, March, and April 2005	Intervention: 1) Sore throat decision rules only 2) Rapid strep test. 3) Sore throat decision rules and rapid strep test. Control: Usual care.	Usual Care vs. Rapid test only % of Visits Where Antibiotics Were Prescribed: 58.2 vs. 26.7; p<0.001
Llor, 2011[65] Patient N= 543 Practice N= 20 Patients (14-60 y); acute pharyngitis Fair quality	Cluster RCT January to May 2008	Intervention: Rapid strep test. Control: Usual care. (Cultures taken in both groups.)	Intervention group vs. Control Inappropriateness of antibiotic prescription according to culture: 26.9% vs. 60.0%; p<0.001 Prescription of antibiotics 43.8 % vs. 64.1%; p<0.001

RCT = randomized controlled trial

Decision Rules

One small fair quality RCT provided low-strength evidence that, compared with usual care, use of a clinical decision rule alone did not statistically significantly reduce family physicians' antibiotic prescriptions for sore throat (55% vs. 58% p=NS).[31] The sore throat decision rule used in the study required antibiotic prescription when physicians rated patients as having met at least three of the following criteria: (1) no cough, (2) Fever above 38 degrees Celsius, (3) swollen submandibular glands, and (4) exudate on throat or tonsils.

Tympanometry

In a fair-quality RCT of 398 children ages 6 to 36 months with suspected AOM, all children underwent tympanometry with results made available to treating physicians in one group and not for the other group.[42] While all physicians in the group received information on interpreting tympanometry results, 59 percent had or were receiving specific training in a fellowship program. Less than 1 percent of patients had unsuccessful tympanometry. This study provided low-strength evidence that 28 percent of the children received a prescription for an antibiotic, with no differences between groups (28.8% with tympanometry results vs. 26.8% without; p=0.62). Serious AOM was diagnosed in 5.8 percent with tympanometry results and 3.2 percent

in the group without these results. Based on physician report, having the tympanometry results available altered the decision to prescribe antibiotics in only 2.8 percent of cases.

System-Level Interventions

Decision Support

Five fair quality RCTs[59,73,74,80,94] and three observational studies[143,145,149] assessed electronic decision support systems as a method to improve antibiotic prescribing for acute RTIs. Two other RCTs rated poor quality and were excluded (Evidence Table 2 [Appendix E]).[58,86] The studies involved intervention groups that received electronic clinical decisionmaking tools compared with no decision support, except one study that also studied a paper decision support system (Table 10).[80] All studies reported comparison of overall antibiotic use between intervention and comparator group but two compared the change in antibiotic use before and after study periods.[80,94] With regard to patient characteristics, one was limited to acute bronchitis among older children and adults,[80] one involved children and adults with acute pharyngitis,[59] one included children and studied a variety of conditions, and the remaining two included any patient with clinical visits for acute RTI.[73,74]

There was variability among the studies with regard to how antibiotic use was defined. Two studies assessed appropriate prescribing; one defined appropriate antibiotic use based on patients with ICD-9 codes for acute bronchitis and then limited to patients ages 13 to 64 years without presence of comorbidities and without antibiotic "responsive" secondary conditions including pharyngitis, sinusitis, AOM, and pneumonia. It is presumed that identification of these conditions was also based on ICD-9 codes alone, not chart review.[80] The other presented clinicians with evidence guiding prescribing in response to the electronic prescription initially entered. Following the evidence-based recommendation was considered appropriate prescribing.[94] The other studies measured overall antibiotic use,[59,73,74] although two reported "appropriate" antibiotic use as a secondary outcome using only ICD-9 coding to determine appropriateness (strep pharyngitis, pneumonia, sinusitis, and AOM).[73,74]

Appropriate Prescribing

Both studies measuring appropriate use found improvements with the electronic systems (Table 10). In the study of patients with acute bronchitis, electronic decision support led to a greater improvement in appropriate antibiotic use compared with control (13% difference; p=0.01) and a paper decision support tool (6% difference), although the difference between electronic and paper was not statistically significant. [80] The other study found that for AOM electronic support via presenting evidence in reaction to initial prescribing resulted in a 24 percent decrease in prescribing of antibiotics against the evidence-based recommendation. [94] As noted in Table 10, the use of the electronic systems was reported as 100% in one study and not reported in the other. The consistency and precision of these fair-quality studies support a moderate-strength evidence of a beneficial effect in improving *appropriate* prescribing.

Overall Prescribing

While three other studies reported inconsistent findings for *overall* antibiotic use, overall antibiotic prescribing was reduced (-9.2%; RR 0.73; 95% CI, 0.58-0.92) in the study reporting the highest level of use of the electronic support system (57%).[94] Two other studies conducted in the same population by the same group of researchers, where use of the system was only 6% or 28%. failed to show any difference in antibiotic prescribing associated with an electronic

intervention in patients with more broadly defined acute RTI (reduction of 0% to 4%).[73,74] In per-protocol analyses limited to instances where the intervention tool was used, some small reductions in antibiotic use were noted within some of the studies. For example, Linder, et al. performed a secondary analysis comparing users and nonusers of the interventional support tool, and there was slight decrease in antibiotic use overall for acute respiratory infections of all types (42% among users vs. 50% among nonusers, p=0.020.[74] Taken together, these studies suggested that use of electronic decision-support might have some effect upon prescribing practice if physicians used them (Table 10). The observational evidence did not provide better evidence or fill gaps in the trial evidence; one found the intervention unsustainable and two found benefit although small.[143,145,149] For electronic decision support systems with greater than 50% use rates, there is low strength evidence of modest reductions in overall prescribing.

Table 10. Studies of electronic decision support and antibiotic prescribing for acute respiratory tract infections

Study and Characteristics	Design and Dates	Intervention and Control Details	Percent Use of System	Outcome
Appropriate Prescribing				
Davis, 2007[94] Patient N = 12,195 (visits) Provider N = 44 AOM Fair quality	Cluster RCT November 1999 – December 2003 (PCC) and June 2002 – December 2003 (SP)	Intervention: evidence-based message system presenting real-time evidence to providers based on prescribing practices. Control: no message system.	100%	% Prescribing according to evidence Change in control vs. intervention (adjusted) AOM: 24% (8%, 40%)
Gonzales, 2013[80] Patient N = N/A Provider N = NR Practice N = 33 PCP sites Acute bronchitis Fair quality	Cluster RCT October 1, 2009 – March 31, 2010 (winter period following intervention, compared to previous 3 winter periods)	Intervention: *Printed decision support*: support for acute cough illness through print-based strategy. *Computer-assisted decision support*: decision support through an electronic medical record-based strategy. Control: no support.	NR	Change in antibiotic use (%) Control: 72.5% vs. 74.3% Printed decision support: 80% vs. 68.3% Electronic decision support: 74% to 60.7%. Control vs. printed support: p=0.003 Control vs. computer support: p=0.01 Printed vs. computer support: p=0.67
Overall Prescribing				
Linder, 2009[73] Patient N = 111,820 Provider N = 443 Acute RTI (undefined) Fair quality	Cluster RCT November 3, 2005 – May 31, 2006	Intervention: EHR-integrated, documentation-based clinical decision support system for the care of patients with ARIs ("ARI Smart Form"). Control: usual care (no decision tool).	6%	% Visits with antibiotic use Control vs. intervention: 39% vs. 43% OR 0.8 (95% CI, 0.6-1.2)

Study and Characteristics	Design and Dates	Intervention and Control Details	Percent Use of System	Outcome
Linder, 2010[74] Patient N = 136,633 Provider N = 573 Pharyngitis, sinusitis, AOM, influenza, acute bronchitis, nonspecific upper respiratory infection Fair quality	Cluster RCT November 27, 2006 – August 31, 2007	Intervention: EHR-based feedback system ("ARI Quality Dashboard"). Control: usual care (no decision tool).	28% at least once	% Visits with antibiotic use Control vs. intervention: 47% vs. 47%
McGinn, 2013[59] Patient N = 1,172 Provider N = 168 Pharyngitis or respiratory infection Fair quality	RCT November 1, 2010 – October 31, 2011	Intervention: Walsh and Heckerling clinical prediction rules; EHR integrated; 1-hour in-person training. Control: usual care + background information on Walsh and Heckerling clinical prediction rules.	57%	% Visits with antibiotic use Control vs. intervention: 29.2 vs. 38.4% (-9.2%); RR 0.73 (95% CI, 0.58-0.92)

[a]Two poor-quality studies not listed above.

Multifaceted Interventions

Combining Multiple Types of Behavioral Interventions Versus No Intervention

Two fair-quality trials and seven observational studies (six fair quality and one poor quality) provided low-strength evidence on the effectiveness of three or more types of interventions on antibiotic use for acute RTI. Five studies included a component of provider education in addition to feedback given to providers about prescribing practices. Additional elements of the interventions included provider communication training,[34,155] peer group feedback or peer review in addition to individual provider reports,[4,82,129,131,132,151] a clinical decision support tool,[139] patient education,[4,129,131,132] or introduction of clinical algorithms.[151]

Appropriate Prescribing

There was low-strength evidence that a multifaceted intervention that combines clinical and provider education components can increase appropriate prescribing by 21.5 percent over usual care in patients with acute RTI. This evidence came from a fair quality, before-after study with a separate control group conducted in Mexico that directly measured the appropriate use of antibiotics based on application of a clinical guideline in accordance with specific, predefined criteria.[151] The intervention involved (1) a clinical algorithm, (2) clinical tutor training, and (3) a three-part educational intervention for physicians including interactive workshops, individual tutorials, and round-table peer-review sessions.[151] Baseline inappropriate prescribing was 78 percent. Compared with baseline, the average increase in appropriate prescribing of antibiotics for the combined intervention was statistically significant while the control group did not show changes (difference in mean proportions: 23; 95% CI, 10 to 35 vs. 1.5; 95% CI, -8.6 to 12, $p<0.05$).

Appropriate prescribing (as defined by CDC guidelines) was also directly measured in a fair-quality before-after study of a more intense multifaceted intervention, ABX-TRIP (The Reducing Inappropriate Prescribing of Antibiotics by Primary Care Clinicians), which combined (1)

electronic decision support with local tailoring and extensive site-based training, (2) audit and feedback, (3) delayed prescribing encouragement; and (4) patient education materials.[139] This was a demonstration project involving nine primary care practices in nine states that are in a practice-based research network (PPRNet), whose members use a common electronic health record. Baseline inappropriate antibiotics use was 41% for adults and 21% for children and was not significantly improved by the multifaceted intervention in either group (Table 11). The electronic decision support system was only used at 6% of the documented encounters, limiting the assessment of the intervention efficacy. This evidence is insufficient to draw conclusions.

Overall Prescribing

2 components: There was low-strength evidence that multifaceted interventions that combine provider education and audit and feedback components do not statistically significantly reduce overall antibiotic prescribing for children with acute RTI. This evidence came from a fair-quality RCT[84] and a fair-quality observational study,[127] both in children with acute RTI (Table 11). The combination of (1) provider education with World Health Organization (WHO) standard treatment guidelines and (2) auditing with scoring led to a trend toward improvement in overall antibiotic prescriptions of 8.5 percent when implemented in Bangladesh in clinics with baseline antibiotic prescription rates of 86 to 90 percent.[127] In the more recent RCT conducted in the US, a combination of (1) 1-hour on-site clinician education session and (2) 1-year of personalized, quarterly audit and feedback only led to a 0.2 percent reduction of antibiotic prescribing, which was smaller than the 1.7 percent reduction seen in the control group. At 6 to 8 percent, baseline antibiotic prescribing rates were already very low in this study population.

3 components: There was insufficient evidence to determine whether a multifaceted intervention that combines (1) provider education, (2) encouragement of delayed prescribing, and (3) peer academic detailing improves overall antibiotic prescribing over usual care in patients with acute RTI. The Norwegian general practice Rx-PAD study (prescription peer academic detailing) was a fair-quality RCT that compared the 3-component intervention as used to reduce (1) antibiotics and (2) anticholinergic effects, long acting benzodiazepines, muscle relaxants, strong analgesics, theophylline, combinations of different cardiovascular drugs, non-steroidal anti-inflammatory drugs in combinations, and three or more concurrent psychotropic drugs.[82] As this comparison was not relevant to this review, the only useful evidence from that study was the before after comparison in the antibiotic group. Although there was a small statistically significant reduction in overall prescriptions since we didn't have a relevant control group to compare it to, we cannot rule out that the change was a function of a temporal trend.

4 components: There was low-strength evidence that multifaceted interventions comprised of 4 components may statistically significantly reduce overall antibiotic prescriptions for some infection types. A combination of (1) education meetings for providers, assistants and pharmacists, (2) communication training, (3) monitoring and feedback on prescribing behavior, and (4) patient education materials was evaluated in the Netherlands for patients with acute RTI based on one RCT[34] and one observational study.[155] Although the RCT found a statistically significant 12 percent reduction in overall antibiotic use, the related observational study that used the same set of interventions did not show an effect.[155] Authors attributed this difference to less rigorous application of the intervention in the observational study than in the trial. Ultimately, this may more accurately reflect the difficulties in applying a multifaceted intervention in a real world setting.

In a series of related observational studies,[4,129,131] the combination of (1) physician education, (2) practice profiling, (3) academic detailing, and (4) patient education proved more effective

than usual care in reducing overall antibiotic use in adults with bronchitis, but not for other RTIs,[4,129] and also not for various RTIs in the elderly[131] or in children with acute pharyngitis.[129] Compared with a limited intervention group that only received office-based patient education materials, the reduction in overall antibiotic prescriptions for the full multifaceted intervention was also significantly greater in adults with bronchitis, but not other RTIs.[4]

Outcomes by Subgroups

Studies on multifaceted interventions provide only limited information about subgroup effects. Only studies of one multifaceted intervention reported their own subgroup analyses, which provided some evidence that the effectiveness of the combination of (1) physician education (2) practice profiling, (3) academic detailing, and (4) patient education varies by type of RTI and age and is greatest in adults with bronchitis.[4,129,131,132]

Age. In adults, the multifaceted intervention reduced overall antibiotic prescribing for bronchitis, but not uncomplicated sinusitis,[4] however in the elderly, the intervention did not significantly reduce overall antibiotic prescribing in bronchitis or sinusitis. The intervention also did not reduce overall antibiotic prescribing in children with acute pharyngitis. This may be attributed to the prevalence of certain bacteria in the pediatric population, clarity on general clinical recommendations and factors other than patient expectations and demands affecting antibiotic treatment decisions in the elderly.

Table 11. Studies of multifaceted interventions compared with usual care

Study and Characteristics	Design and Dates	Infection or Diagnosis	Intervention and Control Details	Outcomes
Appropriate prescriptions				
Litvin, 2013[139] Provider N = 39 Fair quality	Before-After 1/10-3/11, 7/11-3/12	Acute RTI	Intervention: (1) Electronic health records-based electronic decision support with local tailoring and extensive multi-phase, site-based training, (2) Audit and feedback, (3) Delayed prescribing encouragement, (4) Patient education materials. Control: Pre-intervention	Inappropriate antibiotic use: Adults: +1.6% (95% CI, -5.4 to 8.5) Children: -1.9% (95% CI, -9.0 to 5.3)
Reyes-Morales, 2009[151] Patient N=1495 Provider N=106 Fair quality	Controlled Before-After	Acute RTI	Intervention: (1) Clinical algorithm, (2) clinical tutors trained, (3) three-part educational intervention for physicians included interactive workshops, individual tutorials, round-table peer-review sessions. Control: Preintervention.	Appropriate prescription of antibiotics (difference of mean proportions vs. baseline, 95% CI): Workshop: 14 (2.6 to 26) vs. -1.2 (-11 to 8.3) Tutorial: 11 (-0.7 to 23) vs. -4.4 (-14 to 5.3) Peer review: 23 (10 to 35)* vs. 1.5 (-8.6 to 12); p<0.05 vs. control

Study and Characteristics	Design and Dates	Infection or Diagnosis	Intervention and Control Details	Outcomes
Overall prescriptions				
2 components				
Gerber, 2013[84] Patient N = 185,212 Provider N = 162 Practice N = 18 Fair quality	RCT October 2008-June 2011	Acute RTI in children	Intervention: (1) 1-hour on-site clinician education session (June 2010) followed by (2) 1 year of personalized, quarterly audit and feedback of prescribing for bacterial and viral URTIs. Control: usual practice.	Any antibiotic prescribing for viral infections, % before, after, absolute change: Intervention: 7.9%, 7.7%, -0.2% Control: 6.4%, 4.5%, -1.9% Difference of differences: -1.7%; p=0.93
Chowdhury, 2007[127] Practice N = 60 Children <5 Fair quality	Observational Study period NR	Acute RTI in children under 5 years	Intervention: (1) Provider education with WHO standard treatment guidelines, (2) auditing with scoring. Control: no intervention.	Antibiotic prescribing; pre vs. post, absolute difference Intervention: 90.3% vs. 66.6%, -23.7%, p<0.05 for 6/8 sites, p=NR overall Control: 85.9% to 70.7%, -15.2%, p<0.05 for 4/8 sites, p=NR overall Difference of differences: 8.5%
3 components				
Gjelstad, 2013[82] Rx-PAD Patient N = NR Provider N = 382 (79 groups) Fair quality	Before-After 2005 – 2006	Patients with acute RTOs	Intervention: (1) Provider education; (2) delayed prescribing encouraged; (3) peer academic detailing. Control: aforementioned intervention applied to general prescribing in patients > 70 y (excluding antibiotics)	Preintervention: 31.7% Postintervention: 30.4% Change: -1.29 (95% CI, -2.43 to -0.16)
4 components				
Welschen, 2004[34] Patient N = 3,620 Provider N = 89 GPs (12 groups) Fair quality	RCT 2001 – 2002	RTI	Intervention: (1) Education meetings for providers, assistants and pharmacists, (2) communication training, (3) monitoring and feedback on prescribing behavior, (4) patient education materials. Control: No intervention.	Antibiotic prescription rates, % change -4 vs. +8 ; Mean difference of changes (95% CI): -12 (-18.9 to -4.0) -10.7; 95% CI -20.3 to -1.0 Changes in mean number of antibiotic prescriptions per 1000 patients (I vs. C) - 9.7 (p=0.05) vs. + 1.9 (p=0.6)
Smeets, 2009[155] Patient N = NR Provider N = 382 providers (25 groups) Practice N = 141 Fair quality	Observational 2005 – 2007	RTI	Intervention: (1) Education meetings for providers, assistants and pharmacists, (2) communication training, (3) monitoring and feedback on prescribing behavior, (4) patient education materials. Control: No intervention.	Antibiotic prescriptions/1000 patients 2005: +12% vs. +15% (NS) 2007: +13% vs. +12% (NS)

Study and Characteristics	Design and Dates	Infection or Diagnosis	Intervention and Control Details	Outcomes
Gonzales, 1999[4] Patient N = 4,489 Provider N = 93 Practice N = 4 Fair quality	Observational	Various RTI	Intervention: (1) Physician education, (2) practice profiling, (3) academic detailing, and (4) patient education. Control: local control and distant control groups.	Antibiotic Prescribing Rates *Uncomplicated Acute Bronchitis* Full intervention:-26%; 74 vs. 48, 0.003 Control: -2%; 78 vs. 76, 0.81 *Uncomplicated URTIs:* No difference, p>0.05 *Uncomplicated sinusitis*: +2% vs. 0%; No difference, p=0.81
Gonzales, 2004[131] Patient N = 4,270 patient visits Provider N = NR Practice N = 55 (4 intervention, 51 control) Fair quality	Observational	Various RTI in elderly	Intervention: (1) Physician education, (2) practice profiling, (3) academic detailing, and (4) patient education. Control: local control and distant control groups.	Antibiotic Prescription Rates (%) mean change before/after for intervention vs. control: Bronchitis: -8 vs. -3 Sinusitis: -9 vs. -2 URTI: +1 vs. +1
Gonzales, 2005[129] Patient N=16,686 baseline, 14,648 study period Provider N=1,629 baseline, 1,193 study period Practice N=709 baseline, 592 study period Fair quality	Observational	Various RTI	Intervention: (1) Physician education, (2) practice profiling, (3) academic detailing, and (4) patient education. Control: local control and distant control groups.	Adjusted Antibiotic Prescription Rates % change before-after for intervention vs. distal control vs. local control: Children with Acute Pharyngitis: -4% vs. +1 vs. -2; NSD Adults with bronchitis: -24%, p< 0.002 vs. -7% to -10%, p=0.006

NR = not reported, NS = not significant, NSD = no significant difference, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection, WHO = World Health Organization

Point-of-Care Tests Combined with Other Strategies

CRP Combined with Provider-Focused Communication Training

Two fair-quality RCTs provided low-strength evidence that the combination of training in enhanced provider communication plus use of CRP testing statistically significantly reduces overall antibiotic prescribing compared with usual care and communication training alone, but likely not compared with CRP testing alone. The Improving Management of Patients with Acute Cough by C-reactive Protein Point of Care Testing and Communication Training (IMPAC^{3}T) trial involved 20 general practices in the Netherlands and focused on adults who consulted for LRTI with the primary symptom of cough during the winters of 2005 to 2006 and 2006 to 2007.[105] The communication skills intervention involved a 2-hour, face-to-face small group training seminar, preceded and followed by simulated clinical encounters and peer review of colleagues' simulation transcripts. In contrast, the objective of the consortium-supported study (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe [GRACE]) was to assess wider effects of the interventions by targeting a more broad base of patients with both upper and LRTIs who were seen between February and March of 2011 across 259 primary care practices in six European countries.[67] The communication training was internet-based and accompanied by video demonstrations of consultation techniques and an interactive booklet to use during consultations, which the authors suggested may have the potential advantages of accommodating more wide dissemination without requiring on-site highly trained facilitators. Based on our pooled analysis, overall antibiotic prescribing rate was

31 percent in the combination group, which was statistically significantly lower than in the usual care group (59%; OR 0.30; 95% CI, 0.26 to 0.36) and in the group that only received communication training (40%; OR 0.67; 95% CI, 0.56 to 0.78). There was heterogeneity between trials, however, in the comparison between the combination group and the group who received CRP testing alone. In the smaller, earlier IMPAC^{3}T trial, which was limited to patients with LRTI from the Netherlands, the combination intervention statistically significantly reduced overall prescribing rates compared with CRP testing alone (23% vs. 39%; OR 0.47; 95% CI, 0.25 to 0.86), but not in the later, larger, multinational trial of patients with upper and LRTI that used an internet-based method of training delivery (32% vs. 35%; OR 0.87; 95% CI, 0.72 to 1.04). The particular reason(s) for the heterogeneity was unclear as there is variation between these studies on multiple clinical and methodological factors.

Provider and Patient Education Combined with CRP

There was low-strength evidence, based on six fair quality observational studies that, compared with usual care, a multifaceted intervention that combines provider and patient education with use of CRP testing leads to a statistically significant reduction in overall antibiotic prescribing across various infection types compared with provider and patient education alone or control.[122,124,140-142] This evidence came from HAPPY AUDIT studies (Health Alliance for Prudent Prescribing, Yield And Use of Anti-microbial Drugs In the Treatment of Respiratory Tract Infections) involving general practitioners from Spain during the winters of 2002 to 2003[122] and from Denmark, Sweden, Lithuania, Russia, Spain, and Argentina in 2008 and 2009.[124,140-142] Two types of interventions were tested; patient and provider education combined with education on rapid tests in general and access to CRP specifically, compared with combined patient and provider education alone.

The first study reported overall prescription rates before and after the full intervention and for a control group in patients with URTIs and LRTIs seen in Spain during the winters of 2002 to 2003 and evaluated variation across subgroups based on the infection categories of ears, tonsils, pharynx/larynx/trachea, sinuses, and bronchi/lungs,[122] while a later study by this same group evaluated whether changes in prescription rates before and after the full intervention vary across the countries of Denmark, Sweden, Lithuania, Russia, Spain, and Argentina.[124] Three other studies by another group of researchers reported the changes in overall prescription rates before and after the full and partial interventions and in a control group in patients with pharyngitis,[141] rhinosinusitis,[140] and LRTIs.[142] The study of patients with lower respiratory infections also evaluated subgroups of those with acute bronchitis.[142]

The magnitude of reductions in antibiotic prescriptions varied across infection types and the pattern of variation differed between observation periods of 2004 to 2005 and 2008 to 2009 (Table 12). In the study of 2004 to 2005, the greatest reductions with the full intervention were for pharynx/larynx/trachea and bronchi/lungs subgroups.[122] In contrast, for patients seen in Spain from 2008 to 2009, rhinosinusitis was consistently among the top two infection types that had the greatest potential for benefitting from the full intervention, compared with either usual care or the partial intervention. For acute RTI diagnoses, patients with ear infections[122] benefitted the least from the full intervention. The magnitude of the reductions in antibiotic prescriptions for URTIs and LRTIs with the full intervention, respectively, also varied between countries, with the largest seen in Lithuania (20% and 42%) and Russia (15% and 25%), then Spain (9% and 25%), Argentina (5% and 9%), Sweden (+5% and 5%), and Denmark (0% and 2%).[124]

Table 12. Comparison of overall antibiotic prescription rates from Happy Audit studies: proportions of patients (OR [95% CI])

Infection Type (N) Study Period, Location	Education + CRP vs. Usual care[a]	Education alone vs. Usual care[a]	Education + CRP vs. Education alone[a]
Rhinosinusitis (N = 380), 2008 – 2009 in Spain [140]	57% vs. 87%; 0.12 (0.01 to 0.32)	83% vs. 87%; 0.65 (0.21 to 1.01)	57% vs. 83%; 0.27 (0.15 to 0.49)
LRTI (N=2,150), 2008 – 2009 in Spain[142]	Overall: 44% vs. 77%; 0.21 (0.12 to 0.38) Bronchitis: 30% vs. 71%; 0.18 (0.13 to 0.23)	Overall: 56% vs. 77%; 0.42 (0.22 to 0.82) Bronchitis: 41% vs. 71%; 0.28 (0.21 to 0.39)	Overall: 44% vs. 56%; 0.61 (0.50 to 0.74) Bronchitis (N=1469): 30% vs. 41%; 0.63 (0.49 to 0.80)
Pharyngitis (N = 3,646), 2008 – 2009 in Spain[141]	22% vs. 50%; 0.23 (0.11 to 0.47)	47% vs. 50%; 0.53 (0.23 to 1.2)	22% vs. 47%; 0.32 (0.28 to 0.37)
URTI and LRTI (N = 4,136), Winter of 2004 – 2005 in Spain[122]	Overall: 24% vs. 32%; 0.67 (0.58 to 0.77) Pharynx/larynx/trachea (N = 915): 8% vs. 18%; 0.40 (0.24 to 0.62) Bronchi/lungs (N = 1,300): 40% vs. 61%; 0.43 (0.34 to 0.54) Tonsils (N = 228): 49% vs. 68%; 0.45 (0.25 to 0.85) Sinuses (N = 124): 49% vs. 61%; 0.61 (0.28 to 1.36) Ears (N = 262): 42% vs. 25%; 2.17 (1.06 to 4.49)	NA	NA

[a]Postintervention rates

LRTI = lower respiratory tract infection, NA = not applicable, URTI = upper respiratory tract infection

Rapid Strep Testing combined with a Decision Rule

There was low-strength evidence from two fair-quality RCTs that a rapid strep test plus a decision rule can achieve a greater reduction in overall antibiotic prescribing for sore throat than usual care, delayed prescribing, and the decision rule alone, but not the rapid strep test alone..[31,71] The first RCT involved 37 family doctors in eastern Newfoundland and enrolled 533 patients who were seen for sore throat during February to April of 2005. The decision rule in this study involved scoring patients with one point for each of the absence of cough, fever >38 degrees Celsius, swollen submandibular glands, and exudate on throat or tonsils. Scores of 3 to 4 indicated that antibiotics were required. This RCT compared the rapid strep test plus the decision rule to usual care, the rapid strep test only, and the decision rule only. The second RCT involved 48 general practitioners and triage practice nurses in general practices in south and central England who saw people ages ≥3 presenting with acute sore throat (two weeks or less of sore throat) and an abnormal looking throat (e.g., erythema and/or pus) between October 2008 and April 2011.[71] The clinical score used was FeverPAIN, which involved offering immediate antibiotics for score ≥4, delayed antibiotics for scores of 2 to 3, and no antibiotics for scores of 0 to 1. This RCT compared the RADT and decision rule combination to the decision rule only and delayed prescribing. The delayed prescription strategy was to leave the prescription for collection after 3 to 5 days. Findings across the two studies indicated that the combination of rapid strep test plus a clinical score led to significantly lower overall antibiotic prescribing rates compared with usual care (38% vs. 58%; RR 0.66; 95% CI, 0.49 to 0.86),[31] the clinical score alone (EPC pooled rates: 36% vs. 47%; EPC-calculated pooled OR 0.70; 95% CI, 0.50 to 0.98), and delayed prescribing (35% vs. 46%; RR 0.73; 95% CI, 0.52 to 0.98),[71] but not the rapid strep

test alone (38% vs. 27%; RR 1.43; 95% CI, 0.98 to 2.11).[31] Absolute differences in rates were 10 to 11 percent for all comparisons.

Augmentation of Interventions

The second type of multifaceted intervention strategies assessed were those that can be considered augmentation of a primary intervention by adding a second intervention from a different category (e.g., education combined with system-level intervention). Six trials (five fair and one good quality in six publications) provided evidence on whether augmenting one intervention type with a second intervention affects antibiotic prescribing practices (Table 13).[46,55,64,67,68,110] Four reported on overall antibiotic prescribing while two measured appropriate prescribing. One assessed appropriate use of antibiotics based on the following categories: (1) "never indicated" (acute bronchitis and colds/upper RTO); (2) "sometimes indicated" (sinusitis and uncharacterized AOM or pharyngitis); and (3) "always indicated" (streptococcal pharyngitis, AOM, and pneumonia).[46] Categorization was based on chart review and corroboration of clinician diagnoses. The other study defined appropriate prescribing as that which adhered to guidelines developed by the investigators, derived from evidence-based US guidelines endorsed in 2001 by the Centers of Disease Control and Prevention (CDC), the American Academy of Family Physicians, the American College of Physicians, and the Infectious Disease Society of America. In three trials, appropriate use of antibiotics was indirectly measured as it was based mainly on use of antibiotics after a specific period of time following the onset of symptoms.[55,64,68]

A fair quality RCT provided moderate-strength evidence that adding clinical decision support to community education about antibiotic use in children with acute RTIs in rural primary care settings is effective in improving appropriate prescribing and overall prescribing (Table 13).[46] The combined intervention resulted in a 27 percent lower rate of prescribing for the category of diagnoses where antibiotics were "never indicated" (p=0.03) compared with the community education strategy alone. In contrast, a second trial provided low strength evidence that the addition of communication training for clinicians to clinician education does not improve the rate of appropriate prescribing, according to guidelines (Table 13).[110] This study also found no difference between these groups in the rate of overall prescribing for acute RTI.

For the outcome of overall prescribing, two trials assessed the benefit of adding minimal patient education to delayed prescribing techniques with conflicting findings (insufficient evidence).[55,64,68] In a factorial design RCT (N = 807), the addition of a patient educational leaflet to immediate, no, or delayed prescribing for acute illness with cough did not have a significant effect on patient-reported antibiotic use (p=0.58).[55,68] In contrast, an earlier RCT (N = 259) that provided information leaflets to patients in addition to suggested delayed prescribing for acute bronchitis had a significant reduction in antibiotic usage among patients who received the leaflet compared with those who did not (difference 15%).[64] In the first study, patients in the delayed prescription group were required to return to clinic to retrieve the prescription if they felt they needed it after 14 days. Possibly as a result of the added hurdle of returning to clinic to retrieve the prescription, the overall rates of antibiotic use were very low (14%). In the second study, all patients were given a prescription to take home and decide if they needed it and the rate of filling the prescription were much higher (47% vs. 62% in intervention and control groups). These differences may explain the inconsistency of findings.

A fair-quality, multinational, cluster RCT provided low-strength evidence that combined internet training of primary care providers in use of CRP and communication skills resulted in reductions in antibiotic prescribing for acute RTI compared with communication training alone

(32% vs. 41%; p< -0.0001), but that the combination was not superior to CRP training alone (32% vs. 35%; p=0.11).[67]

Outcomes by Subgroups

Diagnosis. One study reported on diagnosis subgroup differences in overall prescription of antibiotics and prescription according to guidelines but the number of events was too low to draw conclusions.[110] In this study, communication training in conjunction with guideline education – compared with guideline education alone – was not associated with any statistically significant differences in overall prescribing for rhinosinusitis (21% vs. 38%; RR 0.56; 95% CI, 0.27 to 1.16), exudative tonsillitis (65% vs. 67%; RR 0.97; 95% CI, 0.54 to 1.73), or bronchitis (24% vs. 20%; RR 1.18; 95% CI, 0.51 to 2.75). It was also not associated with any statistically significant differences in prescribing according to guidelines for rhinosinusitis (12% vs. 24%; RR 0.50; 95% CI, 0.18 to 1.38), bronchitis (5% vs. 5%; RR 1.05; 95% CI, 0.16 to 1.10), or exudative tonsillitis (53% vs. 44%; RR 1.19; 95% CI, 0.51 to 2.81).

Table 13. Randomized controlled trials of augmentation interventions

Study and Characteristics	Design and Dates	Intervention and Control Details	Antibiotic Prescription Use
Appropriate Prescribing			
Samore, 2005[46] Patient N = 407,460 Provider N = 334 Children; acute RTIs Fair quality	Cluster RCT January – December 2001 (preintervention), January 2002 – September 2003 (postintervention)	Intervention: Community education to parents of children <6 y + electronic decision support. Control: community education alone.	Intervention vs. Control Change in prescribing for acute bronchitis and colds/ URTIs (deemed "never indicated") -32% vs. -5% (p=0.03) Overall Antibiotic Use -9.7/100 person-years; p=0.03
Briel, 2006[110] Patient N=552 Practice N=45 Provider N=30 Adults; acute RTI Fair quality	Cluster RCT January – May 2004	Intervention: 6-hour small-group seminar; 2-hour educational training in guidelines; 2-hour personal feedback by phone. Control: educational guideline training only.	Antibiotics prescribed per pharmacists: 13.5% vs. 15.7% adjusted OR 0.86 (95% CI 0.40, 1.93) Reported by clinicians: 15.1% vs. 16.7% adjusted OR 0.90 (95% CI 0.44, 1.98) Antibiotics prescribed according to guidelines: 53.8% vs. 53.1%; adjusted OR 1.03 (95% CI 0.30, 3.09
Overall Prescribing			
Moore, 2009[55] Little, 2005[68] Patient N = 807 Provider N = 37 Age ≥ 3 y; acute cough illness, at least 1 symptom/sign localizing to the lower tract Fair quality	Balanced factorial RCT August 18, 1998 – July 30, 2003	Intervention: Delayed prescribing (prescription available on request if symptoms not resolved after 14 days) + Patient educational leaflet. Control: delayed prescribing only.	Intervention vs. Control Use of antibiotics 55% vs. 57%, (-2%) p=0.58

Study and Characteristics	Design and Dates	Intervention and Control Details	Antibiotic Prescription Use
MacFarlane, 2002[64] Patient N = 259 Provider N = 3 practices Adults; acute bronchitis Fair quality	Nested RCT September 1999 – August 2000	Intervention: Antibiotic prescription with advice to fill if symptoms worsened + information leaflet Control: Suggested delayed prescription alone	Intervention vs. Control % patients taking antibiotics after consultation: 47% vs. 62% (-15%), RR 0.76 (95% CI 0.59 to 0.97)
Little, 2013[67] Europe Patient N = 4,264 Practice N = 246 Adults; acute URTI and LRTIs Fair quality	Cluster RCT October – December 2010 (baseline), February – May 2011 (intervention)	Intervention: Provider internet training on CRP testing and patient management + enhanced communication training. Control: CRP or communication training alone	Combined vs. Communication[a] Unadjusted RR 0.77 (95% CI 0.69 – 0.86) Combined vs. CRP Training Unadjusted RR 0.91 (95% CI 0.81 – 1.02)

[a] Calculated by EPC

CRP = C-reactive protein, LRTI = lower respiratory tract infection, RTI = respiratory tract infection, URTI = upper respiratory tract infection

Key Question 2. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on antibiotic resistance compared with other strategies or standard care?

Key Points

- One small study of watchful waiting reported reducing **resistance** to 4-6 antibiotics compared with immediate prescribing (28% vs 56%; $P<0.02$); however, it was low strength (1 RCT, N=223) and limited to children with acute otitis media.

Detailed Assessment

Watchful Waiting

A fair-quality RCT of 223 children with nonsevere AOM comparing watchful waiting and immediate prescribing provided low-strength evidence that *S pneumonia* strains cultured from children in the immediate antibiotic group at day 12 were more likely to be multi-drug resistant (number of antibiotics: 0: 30% vs. 0%; 1-3: 42% vs. 44%; 4-6: 28% vs. 56%; p<0.02) while there were no difference at baseline.[60] The study also reported resistance to penicillin as significantly lower in the watchful waiting group (67% vs. 89%; p<0.04).

No other study reported on the impact of an intervention on antibiotic resistance rates relative to other interventions or to no intervention. One study of rapid strep testing reported on the specific resistance rates for isolates of S. pyogenes found in throat cultures of study participants but did not report these by intervention group.[61]

Key Question 3. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on medical complications (including mortality, hospitalization and adverse effects of receiving or not receiving antibiotics) compared with other strategies or standard care?

Key Points

Educational Interventions

- Low-strength evidence suggested that educational interventions did not adversely affect medical complications as a result of decreased antibiotic prescribing for acute RTIs.

Clinical Interventions

Delayed Prescribing Strategies

- Delayed compared with immediate prescribing: There was low-strength evidence of no significant difference in complications. There was low-strength evidence that the only difference in adverse drug effects is a decrease in diarrhea in AOM.
- Different strategies of delaying prescriptions: There was low-strength evidence of no significant differences in complications, diarrhea or rash, but giving prescriptions with instructions to delay had a higher rate of vomiting than with leaving prescriptions for collection and a higher rate of abdominal pain compared with requiring recontact.

Procalcitonin Point-of-Care Testing

- In adults, low-strength evidence suggested that use of a procalcitonin algorithm did not significantly affect mortality or treatment failure at 30 days in primary care or ED patients with acute bronchitis, URTI, or presenting to primary care with upper or lower acute RTI.
- In children with suspected AOM, low-strength evidence suggested that use of an adult procalcitonin algorithm does not significantly affect a composite outcome measuring adverse events and lack of efficacy (OR 1.21; 95% CI, 0.52 to 2.85) or hospitalizations (OR 1.41; 95% CI, 0.68 to 2.93). Adverse effects associated with antibiotic use were more frequent with use of the algorithm than with procalcitonin (OR 3.03; 95% CI, 1.11 to 9.22).

System-Level Interventions

- There was low-strength evidence that between electronic decision support, a paper-based support tool and usual care in patients with uncomplicated acute bronchitis of results in similar rates of pneumonia diagnoses or 30-day hospitalizations.

Point-of-Care Tests Combined with Other Strategies

- There was low-strength evidence that the combination of training in enhanced provider communication plus use of CRP testing may increase risk of hospitalization compared with usual care, but not when compared with either intervention alone, regardless of the methods of training delivery.

Detailed Assessment

Educational Interventions

For the intervention strategy of education, two studies reported outcomes that are related to medical complications that may be associated with not using antibiotics in acute RTIs.[130,154,167] A large study of a public media campaign, aimed largely at parents of young children, found no statistically significant differences in diagnosis of several conditions identified as potential complications of acute RTIs, including pneumonia, peritonsillar abscess, retropharyngeal abscess, and epiglottitis using managed care organizations' administrative data from in the intervention and control cities before and after the intervention period.[130] An observational study (N = 819 children age 1-15 years) conducted in Norway in the late 1990's used both clinician and parent education aimed at reducing prescribing for AOM, using an evidence-based symposium and written guideline plus patient pamphlets and verbal information.[154] The study reported on the incidence of mastoiditis as a consequence of inappropriately withholding antibiotics for bacterial AOM but no cases were reported during the baseline or study periods. These studies provided low-strength evidence of no difference in the incidence of medical complications to draw conclusions about the potential impact of educational interventions on medical complications of acute RTI.

Communication Interventions

Strategies to Improve Communication between Clinicians and Patients

Of the seven trials that studied interventions to improve communication between clinicians and patients regarding the use of antibiotics for acute RTIs (Evidence Table 1 [Appendix D]), only one fair-quality study assessed the outcome of hospitalization.[67] It found that slightly more patients treated by clinicians who received the communication intervention only were hospitalized within 4 weeks after the clinic visit (0.5%; 6/1101) compared with the usual care group (0.2%; 2/861), but the difference was not statistically significant (RR 2.35; 95% CI, 0.48 to 11.60).[67] When compared with patients in clinics using point-of-care CRP testing, fewer patients in the communication intervention group were hospitalized (0.5% [6/1101] vs. 1.0% [10/1018]; RR 0.56; 95% CI, 0.20 to 1.52), which was also not statistically significant. The small size and relatively low quality of the single study prevents firm conclusions.

Clinical Interventions

Delayed Prescribing Strategies

Delayed Compared with Immediate Prescribing

For adverse drug effects, the Cochrane review analyzed rates of diarrhea, rash, stomach ache, and vomiting, but did not pool results for any of these outcomes due to significant heterogeneity, which authors stated was likely due to the differences in types of antibiotics prescribed for each clinical condition.[14] For diarrhea, there was low-strength evidence that the only difference in antibiotic prescribing strategies is that, compared with immediate antibiotics, a delayed prescribing strategy significantly reduces diarrhea in children with AOM (8% vs. 21%; our pooled OR 0.35; 95% CI, 0.21 to 0.59).[41,72] Otherwise, based on meta-analyses presented in the Cochrane review, there was no significant difference in diarrhea between delayed prescribing

and immediate antibiotics in adults and children with cold (16% vs. 19%; OR 0.82; 95% CI, 0.33 to 2.02)[117] or in adults and children with sore throat (13% vs. 11%; OR 1.23; 95% CI, 0.67 to 2.28).[66] For the outcome of rash, there is low-strength evidence of no difference between delayed and immediate antibiotic prescriptions in children with AOM (5% vs. 4%; OR 1.21; 95% CI, 0.41 to 3.58)[72] and in adults and children with sore throat (6.1% vs. 6.5%; OR 0.93; 95% CI, 0.41 to 2.11).[66]

Different Strategies for Delaying Prescriptions

For patients with acute RTIs judged not to need immediate antibiotics, there was low-strength evidence that of no difference between different strategies of delaying prescriptions in complications, but some differences in adverse drug effects. This evidence came from a fair-quality RCT of 433 patients seen across 25 primary care practices between March 2010 and March 2012 in the United Kingdom that compared giving prescriptions with instructions, leaving prescriptions for collection, postdating prescriptions, or requesting recontact, respectively.[70] Complication rates increased as the barriers to getting a prescription increased (0 percent for giving prescriptions with instructions, 1 percent for leaving prescriptions for collection, 0.9 percent for postdating prescriptions, and 3.7 percent for requesting recontact)but none reached statistical significance, although the difference between requesting recontact and leaving prescriptions for collection came closest (p=0.0619). For diarrhea, the largest difference was between giving prescriptions with instructions (21%) and requesting recontact (7%), but it did not reach statistical significance (p=0.0667). For rash, the largest difference was between giving prescriptions with instructions (9%) and leaving prescriptions for collection (2%) but it did not reach statistical significance (p=0.23). Vomiting rate was 18 percent in the group given prescriptions with instructions, which was statistically significantly greater than in the group left prescriptions for collection (4%; p=0.0447), but similar to the group given postdated prescriptions (18%) or in which recontact was requested (10%). Abdominal pain rate was 31 percent in the group given prescriptions with instructions, which was statistically significantly greater than in the group where recontact was requested (10%; p<0.0001), but similar to in the groups given postdated prescriptions (18%) and who were left prescriptions for collection (29%).

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

Two fair-quality trials that studied point-of-care CRP testing for acute RTIs assessed the outcome of hospitalization[67,81] (Evidence Table 1 [Appendix D]). The studies reported on a small number of events and provide insufficient information to assess the strength of evidence.

One trial compared the effectiveness of a clinical algorithm with and without CRP testing as part of the algorithm.[81] The algorithm was used in an urban ED to guide chest x-ray and antibiotic treatment decisions for acute cough illness. The study found a nonstatistically significant higher proportion of patients who were hospitalized when CRP testing was included as part of the algorithm compared with use of the clinical algorithm alone [6 percent (4/68) vs. 3 percent (2/60); unadjusted RR 1.77; 95% CI, 0.34 to 9.30; p=0.68].

The second trial found a higher proportion of patients treated by clinicians who received the CRP training were hospitalized within four weeks after the clinic visit (1.0%; 22/2159) compared with those in the group without CRP test training (0.4%; 8/1962), a difference of borderline significant when adjusted for clustering for communication training received by some clinicians and other confounders (adjusted RR 2.91; 95% CI, 0.96 to 8.85; p=0.06).[67]

Procalcitonin Point-of-Care Testing

In the systematic review (two publications) of procalcitonin algorithms used to help identify appropriate patients for antibiotic treatment in adults, mortality at 30 days was not affected in the primary care setting, where mortality rates were very low (0 of 507 algorithm patients and 1 of 501 control patients; OR 0.32; 95% CI, 0.01 to 7.98).[162,163] This review also found that there were no differences between groups in mortality when stratified by diagnosis of URTI (0 of 282 vs. 1 of 267) or acute bronchitis (0 of 249 vs. 2 of 282). Evidence on mortality was low strength.

A composite measure of "treatment failure at 30 days" was also not different between groups in the primary care setting (OR 0.94; 95% CI, 0.72 to 1.22). In this review, treatment failure in primary care was defined as death, hospitalization, acute RTI-specific complications (e.g., empyema for lower ARIs, meningitis for upper ARIs), recurrent or worsening infection, and still having acute RTI-associated discomfort at 30 days. Limiting this analysis to patients diagnosed with URTI did not alter the findings in a meaningful way (OR 0.95; 95% CI, 0.73 to 1.24). This evidence was low strength.

The single good quality trial of using procalcitonin in children (ages 1 to 18 years) with LRTI provided low-strength evidence of a higher incidence of antibiotic adverse events in patients in the procalcitonin group the control group (26% vs. 10%, 16% absolute difference; OR 3.03; 95% CI, 1.11 to 9.22).[116] This corresponds to the increased prescribing of antibiotics in the procalcitonin group. These adverse effects lasted a mean of 1.0 days in the procalcitonin group and 0.5 days in the control group, but this difference could have been affected by the repeat procalcitonin testing at days 3 and 5.

This study also provided low-strength evidence that the rate of hospitalization was not statistically significantly different between the groups (62% vs. 53%; OR 1.41; 95% CI, 0.68 to 2.93). Duration of hospitalization was also not different (2.5 and 2.3 days [mean], respectively). The duration of hospitalization should also be considered in the light of repeated procalcitonin testing at days 3 and 5, which may have altered the course of continued antibiotic treatment. Using a composite measure, termed "safety", to measure both efficacy and adverse events (serious adverse events, disease-specific failure including hospitalization, recurrent infection requiring antibiotics, comorbidity requiring antibiotics, or worsening impairment of daily activity by $\geq$ 20%), there was low-strength evidence of no difference between groups of patients with non-CAP LRTI diagnoses (OR 1.21; 95% CI, 0.52 to 2.85).

System Level Interventions

One system level study provided low strength evidence of no difference in medical complications with electronic decision support compared with usual care or a paper-based support tool. In a trial of electronic decision support, there was no difference in the proportion of uncomplicated acute bronchitis patients who returned for a second physician visit within 30 days after their initial encounter and who were diagnosed with pneumonia. Similar proportions of patients, between 0.5 percent 1.5 percent, across the study groups returned for such care and were found to have pneumonia. There was no statistical difference between the groups.[80] Hospital admissions within 30 days were rare, with between 0-0.1 percent patients returning across intervention or control sites.

Multifaceted Interventions

Point-of-Care Tests Combined with Other Strategies

There was low-strength evidence that the combination of training in enhanced provider communication plus use of CRP testing may increase risk of hospitalization compared with usual care, but not when compared with either intervention alone, regardless of the methods of training delivery. The IMPAC^{3}T trial and the GRACE consortium-supported trial (both described in Key Question 1 above) both reported rates of hospitalization for adults seen for upper[67] and LRTs by providers who were trained in CRP testing use, enhanced communication skills, or both, or who did not receive any training (usual care). The interventions differed in the method of training delivery, which was internet-based in the GRACE consortium trial[67] and conducted in small-groups on a face-to-face basis in the IMPAC^{3}T trial.[106] Based on our pooled analysis, hospitalization rate was 1.1 percent in the intervention group, which was statistically higher than in the usual care group (0.2%; OR 4.65; 95% CI, 1.21 to 17.87), but similar to the CRP alone group (1.0%; OR 1.07; 95% CI, 0.49 to 2.33) and the communication-alone group (0.48%; OR 2.17; 95% CI, 0.85 to 5.50).

Key Question 4. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on other clinical outcomes (e.g., health care utilization, patient satisfaction) compared with other strategies or standard care?

Key Points

Educational Interventions

- Low-strength evidence suggested that there is no difference in return visits for the index episode of acute RTI with educational interventions and moderate-strength evidence suggested that patient education results in fewer overall clinic or ED visits for acute RTI in the year following the intervention compared with usual care.
  - The best evidence, a good-quality RCT found a 44 percent ($p<0.002$) reduction in "unnecessary" visits for URTIs and no difference in "necessary" visits based on clinical criteria. Results were similar across subgroups of age, race and insurance.
- Low-strength evidence suggested that patient or combined patient/clinician education interventions do not lead to differences in patient or parent satisfaction with clinic visits for acute RTI.

Communication Interventions

- There was low strength evidence that communication interventions resulted in longer duration of symptoms, but better ratings of health at two weeks compared with usual care.
- In head-to-head comparisons, there was low strength evidence that communication skills training and training and use of CRP testing resulted in similar rates of reconsultation and symptom resolution.

Clinical Interventions

Delayed Prescribing Strategies

- Delayed compared with immediate: Compared with immediate prescribing, although delayed prescribing was associated with reduced satisfaction (low strength) and increased persistence of moderate to severe symptoms (low strength), it did not increase short-term or long-term reconsultation behavior. In fact, delayed prescribing may reduce return clinic visits in some cases, especially in patients with a history of receiving antibiotic prescriptions (low strength). We found no studies that compared ED visits or quality of life between delayed and immediate prescribing.
- Different strategies of delaying prescriptions: There was low-strength evidence that there are no statistically significant differences in duration of moderately bad symptoms, reconsultations, or proportions of patients who were very satisfied with the consultation.
- Delayed prescribing versus clinical score: There was low-strength evidence that delayed prescribing leads an additional day of moderately bad or worse symptoms in patients with sore throat, but does not increase return visits before or after 1 month.

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

- Low strength evidence from a pooled analysis of three fair quality trials shows a greater risk of reconsultation within four weeks with a CRP testing intervention compared with usual care (RR 1.36; 95% CI 1.05 to 1.76).
- Low strength evidence from four fair-quality trials that there is no significant difference in the effect of CRP testing on improvement of patients' symptoms or speed of improvement of symptoms compared with usual care.
- In head to head comparisons, low strength evidence from two trials found no effect of CRP testing on improvement of patients' symptoms compared with training in communication skills.
- In a head to head comparison, low strength evidence from one large, fair quality trial suggested a lower rate of reconsultation in a CRP group compared with a communication skills training group.

Procalcitonin Point-of-Care Testing

- Low-strength evidence suggested no differences between using and not using a procalcitonin algorithm in adults presenting to primary care with an URTI or LRTI in the number of days with limited activity or missing work and patients with continuing symptoms at 28 days postbaseline. Evidence was insufficient to draw conclusions on quality of life, burden of illness.

Viral and S. pneumococcal (Rapid strep tests) Point-of-Care Testing

- No studies.

System-Level Interventions

- There was low strength evidence of no difference in ED visits and return outpatient clinic visits between electronic decision support and usual care.

Multifaceted Interventions

- There was low-strength evidence of similar 1-month clinic attendance rates for patient education plus a physician-centered quality improvement project compared with usual care.
- Rapid streptococcal antigen detection test added to a decision rule: There was low-strength evidence that the combination of a rapid streptococcal antigen detection test plus a decision rule has comparable effects on symptom improvement and return visits compared with use of the clinical score alone or delayed prescribing.
- CRP plus provider-focused communication training: Compared with either intervention alone, there was low-strength evidence of comparable days of moderately bad symptoms, reconsultation rates, diagnostic testing use and days off work. Compared with usual care, there was a longer duration of moderately bad symptoms, but comparable reconsultation rates, diagnostic testing use, and days off work.

Detailed Assessment

Educational Interventions

Five studies of educational interventions reported on outcomes of additional healthcare utilization and patient satisfaction.[47,56,120,130,167] In the short term, two cluster RCTs found no difference in the rate of return visits following educational interventions, although statistical power for this outcome was not assessed in either study and the absolute differences are inconsistent across the studies. The good-quality study using an interactive booklet during clinic visits found no statistically significant difference in return visits within 2 weeks compared with usual care (12.9% vs. 16.2%, OR 0.75; 95% CI, 0.41 to 1.38).[167] A fair-quality trial using a combination of clinician and adult patient education, including an ED waiting room computer kiosk, also found no difference between groups in return visits to the ED within 2 weeks, based on patient report. The proportion reporting they had returned increased from preintervention to postintervention more in the control group (5% vs. 1%; p=0.48).[56]

Additionally, two studies using patient or parent education examined new office or ED visits and found the impact of the interventions to be beneficial over longer time periods.[47,130] One large, fair quality, observational study of a public media campaign found a reduction in subsequent visits (over 12 months) for children with a broad range of acute RTIs (p=0.01, point estimate for magnitude not reported).[130] Fairly large differences between the intervention and control cities in baseline office visits (net difference range 3 to 24 per 1000 persons per month in baseline year) were controlled for in the analysis (postintervention range of net differences were +10 to -15 per 1000 persons per month). The largest differences occurred near the end of the campaign period (late-winter/early spring) and then during the winter months. This study found no differences in adult visits for acute RTIs, but the intervention was loosely aimed at parents of young children. A good-quality RCT focused a pamphlet-based intervention only on reducing visits for URTI in adults or children and found significant reductions in visits (11 to 17 months after randomization) for URTI overall (-29%; p<0.01) as well as those deemed unnecessary (-44%; p<0.002).[47] The study team developed a list of criteria to differentiate URTIs that necessitate an office visit versus those that do not, for example any oral temperature above 103 degrees Fahrenheit. This study used careful methods to evaluate each case, and families who received/did not receive the intervention were followed up directly. No difference was seen in

visits for necessary URTIs, or for AOM or other respiratory illnesses. Similar results were found across subgroups based on age, race and insurance.

Two cluster RCTs also reported patient satisfaction at 2 weeks of followup. The study of education patients/parents found no difference between groups in satisfaction with the visit (OR 0.64; 95% CI, 0.33 to 1.22), feeling reassured after the visit (OR 0.84; 95% CI, 0.57 to 1.25), or feeling enabled by what they had learned during their visit (OR 1.20; 95% CI, 0.0.84 to 1.73). [167] The second study, using a combination of clinician and patient education, also found no difference in patient satisfaction 2-weeks post index visit, using a 5-point scale (p=0.76).[56]

Communication Interventions Versus Usual Care

Of the seven trials that studied interventions to improve communication between clinicians and patients regarding the use of antibiotics for acute RTIs (Evidence Table 1 [Appendix D]), five fair-quality studies reported on clinical outcomes other than use of antibiotics or medical complications (Table 14).[67,75,76,104-106,110] Relevant outcomes from a single trial were reported in three separate studies.[104-106] The studies assessed a variety of other clinical outcomes, including return clinic visits/reconsultation,[67,76,104,105,110] improvement in symptoms/speed of improvement,[67,75,106,110] patient satisfaction,[105,110] and quality of life.[76] All interventions targeted clinicians only, and used cluster randomization at the level of the clinic or the clinician. Two trials studied interventions specifically designed to improve shared decisionmaking, an approach in which the values, preferences and opinions of both the patient and the clinician are made explicit and considered in the decision.[75,76] Two trials[67,104-106] were factorial designs that assessed two interventions – one to enhance clinicians' communication skills and one to train clinicians in the use of point-of-care CRP testing. All but one intervention involved some form of in-person training by study personnel, while the fifth[67] included an internal practice-based meeting on prescribing issues. One intervention was mostly internet-based[67] and two others included some video or internet-based training.[75,76]

Return Clinic Visits or Reconsultation

Four trials reported on the outcome of return clinic visits or reconsultation.[67,76,104,105,110] These studies varied somewhat in their definitions of reconsultation, with one specifying "repeat consult for the same reason",[76] one specifying "reconsultation for new or worsening symptoms",[67] one specifying repeat visits for subsequent RTIs during more than 3 years of followup,[104] and two not specifying.[105,110] In a factorial design trial,[67] the reconsultation outcome was part of a composite outcome, "new or worsening symptoms" that included reconsultation for new or worsening symptoms, new signs, or hospital admission, as determined by medical record review. Although reconsultations were not reported separately, 96 percent (730/760) of all patients with data on "new or worsening symptoms" had a reconsultation, with the remaining 4 percent having had hospital admissions. Two studies ascertained reconsultation at 2 weeks,[76,110] two studies at 4 weeks,[67,105] and one study at an overall mean of 3.67 years of followup.[104]

Evidence from three trials was insufficient to draw conclusions regarding the impact on communication interventions compared with usual care.[67,76,104,105] Pooling these data resulted in a high degree of heterogeneity, so is not presented ($I^2 = 89\%$). Two trials found an increased reconsultation in groups receiving communication interventions. In the smaller of those trials the effect was not statistically significant (adjusted RR 1.3; 95% CI, 0.7 to 2.3).[76] In the second and larger trial, the effect was borderline significant in a comparison of all patients who received the communication intervention versus those who did not, while adjusting for CRP testing (adjusted

RR 1.33; 95% CI, 0.99 to 1.74).[67] In the same study, the effect was significant in an unadjusted comparison of the communication only group with the usual care group (unadjusted RR 2.12; 95% CI, 1.41 to 3.02).[67] This study – predominantly aimed at patients with LRTIs (80%), but including patients with URTI (20%) – found the increased relative risk of reconsultation among intervention group patients compared with usual care to be higher in those with URTI (adjusted RR 1.72; 95% CI, 0.96 to 2.86) than in those with LRTI (adjusted RR 1.28; 95% CI, 0.97 to 1.66), but with overlapping confidence intervals. The third trial found a decreased risk of reconsultation within 28 days (unadjusted RR 0.75; 95% CI, 0.57 to 1.00; p=0.14, p-value from a model adjusted for CRP testing)[105] and a lower mean number of visits for subsequent RTIs per patient per year during a mean followup of 3.67 years (0.36 vs. 0.57; p=0.09).[104]

Improvement of Patients' Symptoms or Speed of Improvement of Symptoms

Four trials reported on the outcome of improvement of patients' symptoms or speed of improvement of symptoms.[67,75,106,110] These studies each assessed improvement of patient symptoms with a variety of different outcome measures, and found inconsistent effects overall. Three trials provided low-strength evidence that communication interventions resulted in longer duration of symptoms, but better ratings of health at two weeks compared with usual care.[67,75,106] In these studies, the various interventions were associated with: an increase in the proportion of patients who felt their health to be stable or improved at 2 weeks (mean difference 9%; p=0.08);[75] a statistically nonsignificant worse symptom severity score (mean difference 0.06, on a scale of 1-4; p=0.357);[67] prolonged time to resolution of symptoms rated as moderately bad or worse (median days: 6 vs. 5; adjusted HR 0.79; 95% CI, 0.67 to 0.92);[67] and no difference in mean number of days off of work (3.37 [SD 4.02] vs. 3.37 [SD 3.77]).[106]

As with other outcomes, a factorial design trial reported on differences according to lower LRTI versus URTI. They found no difference in mean symptom severity score between the communication and usual care groups in patients with LRTIs (1.83 vs. 1.84; p=0.775); but did find a worse mean score for the communication group in patients with URTI (1.69 vs. 1.44; p=0.044).[67] While moderately bad symptoms were slower to resolve among the communication group compared with the usual care group overall, this difference was more pronounced in patients with URTI than in those with LRTI. In the subgroup with LRTI, the difference in median days to resolution between communication group and usual care was the same as in the overall group (6 vs. 5; adjusted HR 0.83; 95% CI, 0.70 to 0.99) while in those with URTI the difference was greater (5 vs. 3.5; adjusted HR 0.66; 95% CI, 0.48 to 0.89).

Patient Satisfaction

One trial reported on patient satisfaction with a communication intervention compared with usual care.[105] The study (N = 431) reported on the proportion of patients who were at least "very satisfied" and found no difference between the communication intervention and usual care (79% vs. 74%; unadjusted RR 1.06; 95% CI, 0.95 to 1.18).

Quality of Life

Quality of life was reported in a single study (N = 359), providing insufficient information to assess the strength of evidence.[76] The investigators used the SF-12 survey to assess patients' physical and mental quality of life. They found no statistically significant difference between the communication and usual care groups in scores for either the physical or mental scale. The

communication group had a slightly higher mean score on the physical scale (49.4 vs. 48.2) and a slightly lower mean score on the mental scale (50.8 vs. 51.2).

Use of Other Diagnostic Tests

Only one trial (N = 431) reported the effect of a communication skills training intervention on the use of other diagnostic testing compared with either usual care, resulting in insufficient strength of evidence to draw conclusions.[106] The study reported on a small number of events and found no significant differences between the CRP group and usual care in the use of: chest x-ray (5% vs. 7%), blood testing (1% vs. 0%), or other tests such as spirometry or sputum analysis (0% vs. 2%).

Communications Interventions Versus C-reactive Protein Testing (Head-to-Head Comparisons)

Return Clinic Visits or Reconsultation

Low-strength evidence from one large fair-quality factorial design trial (n=2119) indicated no difference in reconsultation in a communication skills training group compared with a group trained in CRP testing (20.3% vs. 23.5%; unadjusted RR 0.94; 95% CI, 0.80 to 1.10) (Table 14).[67] This trial also reported on differences according to lower LRTI versus URTI.[67] Evidence from one trial (n=552) provided insufficient information to assess the strength of evidence regarding a communication intervention in conjunction with prescribing guideline education compared with the education component alone (Table 14).[110] This study found no association of the communication intervention with reconsultation within 14 days (adjusted RR 0.97; 95% CI, 0.78 to 1.21).

Improvement of Patients' Symptoms or Speed of Improvement of Symptoms

Low-strength evidence from two trials found no effect of training in communication skills on improvement of patients' symptoms compared with CRP testing (Table 14).[67,106] These studies each used a different intervention and assessed improvement of patient symptoms or speed of improvement of symptoms with various outcome measures. They found no significant differences between CRP testing and communication training in the outcomes of: mean days off of work (3.37 vs. 3.35);[106] symptom severity score (1.81 [SD 1.02] vs. 1.70 [SD 1.00]):[67] or median number of days to resolution of symptoms (6 [IQR 3:10] vs. 5 [IQR 3:8]).[67]

Evidence from one trial (N = 552) provided insufficient information to assess the strength of evidence regarding a communication intervention in conjunction with prescribing guideline education compared with the education component alone (Table 14).[110] This study found a statistically nonsignificant reduction in the mean number of days with restricted activity (6.18 vs. 6.81; adjusted mean difference 0.40; 95 % CI, 1.07 to 0.27), and no difference in the proportion of patients being off of work within 14 days (OR 1.00; 95% CI, 0.63 to 1.57).[110]

Patient Satisfaction

Patient satisfaction was reported in a study (N = 552) that compared a communication intervention in conjunction with prescribing guideline education versus the education component alone.[110] The study assessed the proportions of patients with a maximum score of 70 (scale 14 to 70) on a patient satisfaction measure, using that outcome because the scores were highly skewed. They found no difference between the communication/education and education only groups in

the proportion of patients with a maximum satisfaction score (47.8% vs. 49.0%; adjusted OR 1.00; 95% CI, 0.64 to 1.31).[110]

Use of Other Diagnostic Tests

Only one trial (N = 431) reported the effect of a communication skills training intervention on the use of other diagnostic testing compared with CRP testing, resulting in insufficient strength of evidence to draw conclusions.[106] The study reported on a small number of events and found no significant differences between the CRP group and communication skills training for the same outcomes: chest x-ray (5% vs. 5%), blood testing (1% vs. 1%), and other tests (0% vs. 2%).

Table 14. Interventions to improve communication between clinicians and patients: Key Question 4 outcomes

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Briel, 2006[110] Practice N = 30 Provider N = 30 Patient N = 552 Patients ≥ 18 y; acute RTI Fair quality	Cluster RCT (clinic level). January 2004 – May 2004 Followup: 14 days	Intervention: *Communication* + *Education*: 6-hour small-group seminar in patient-centered communication; Two-hour educational training in guidelines adapted by investigators; Two-hour personal feedback by phone after intervention. *Education only*: Educational intervention on guidelines, only (2-hour training). Control: no intervention (nonrandomized).	Communication + Education vs. Education only: Reconsultation within 14 days: 44.7% vs. 49.3%; adjusted RR (95% CI): 0.97 (0.78-1.21). Days with restricted activities (mean): 6.18 vs. 6.81; adjusted difference: -0.40 (95% CI -1.07-0.27). Patients off work within 14 days: 53.4% vs. 47.2%; adjusted OR (95% CI): 1.00 (0.63-1.57). Patients with satisfaction score of 70 out of 70 (%): 47.8% vs. 49.0%; adjusted OR (95% CI): 1.00 (0.64-1.31).
Cals, 2009[105] Practice N = 20 Provider N = 40 Patient N = 431 Adults; suspected LRTI and cough < 4 weeks Fair quality	2 X 2 factorial cluster RCT (clinic level). September 2005 - March 2006 and September 2006 - March 2007. Followup: 28 days for most patients (maximum 10 weeks).	Intervention: *Communication skills training*: based on 11 key tasks (e.g., exploring patient's fears and expectations, asking patient's opinion of antibiotics), and elicit-provide-elicit framework. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual Care	Communication + Combination vs. CRP + Control: Reconsultation within 28 days: 27.8% vs. 37.0%; unadjusted RR 0.75, 95% CI 0.57 to 1.00; p=0.14 (p-value from model adjusted for practice level). Patient satisfaction (% at least very satisfied): 78.7% vs. 74.4%; unadjusted RR 1.06, 95% CI 0.95 to 1.18; p=0.88 (p-value from model adjusted for practice level).

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Cals, 2011[106] (see Cals, 2009[105])	See Cals, 2009[105]	See Cals, 2009[105] (above)	Days off of work, days (SD): Communication vs. Control: 3.37 (4.02) vs. 3..37 (3.77) Communication vs. CRP: 3.37 (4.02) vs. 3..35 (4.54) Use of other diagnostic testing: Chest X-ray: Communication vs. Control: 5% vs. 7% Communication vs. CRP: 5% vs. 5% Blood tests: Communication vs. Control: 1% vs. 0% Communication vs. CRP: 1% vs. 1% Other (spirometry, sputum): Communication vs. Control: 0% vs. 2% Communication vs. CRP: 0% vs. 2%
Cals, 2013[104] (see Cals, 2009[105]) Patient N = 379	See Cals, 2009[105]	See Cals, 2009[105] (above)	Office visits for RTIs during followup (mean overall followup of 3.67 years), Mean No. per patient per year (95% CI): Communication + Combination vs. CRP + Control: 0.36 (0.30 to 0.42) vs. 0.57 (0.46 to 0.69), p=0.09 (p-value from model adjusted for practice level).
Légaré, 2010[75] Practice N = 4 Provider N = 33 Patient N = 459 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2007 – March 2008 Followup: 2 weeks	Intervention: Interactive workshops on URTIs, risk communication, fostering patient participation in decisionmaking, shared decisionmaking support tools. Control: Delayed intervention.	Patients who felt they had 'stable', 'a little better' or 'much better' health at 2 weeks (compared with 'not much worse' or 'much worse'): Baseline: 87% vs. 91% After experimental group received intervention (Time 1): 94% vs. 85% After control group received intervention (Time 2): 94% vs. 91% Difference at Time 1 (95% CI): 9 (-2 to 18), p=0.08.
Légaré, 2012[76] Practice N = 9 Provider N = 149 Patient N = 359 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2010 – April 2011 Followup: 2 weeks	Intervention: 2-hour online tutorial and 2-hour onsite interactive workshop on decisionmaking about antibiotic treatment for RTIs and communication with patients. Control: Usual care.	Reconsultation for same reason: Baseline: 21.6% vs. 13.4% After intervention: 22.7% vs. 15.2% Adjusted RR (95% CI): 1.3 (0.7-2.3). Patient QOL (physical scale, 0-100): Baseline: 49.3 vs. 47.7 After intervention: 49.4 vs. 48.2 Mean difference: 0.4 (95% CI -2.6 - 3.3). Patient QOL (mental scale, 0-100): Baseline: 51.2 vs. 48.5 After intervention: 50.8 vs. 51.2 Mean difference: -1.9 (95% CI -4.9 - 1.1).

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Little, 2013[67] Practice N = 228 Provider N = 372 Patient N = 4,121 Patients > 18 y; acute RTI (upper or lower) Fair quality	2 X 2 factorial cluster RCT (clinic level). February 2011 – May 2011. Followup: 4 weeks	Interventions: *Communication skills training*: Internet-based training in communication skills; interactive booklet; video demonstrations. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual care.	Reconsultation for new or worsening symptoms within 4 weeks (composite outcome including hospital admissions, of which 3.9% (30/760) overall was hospital admission): Communication + Combination vs. CRP + Control: 20.1% vs. 16.4%; adjusted RR (95% CI): 1.33 (0.99 to 1.74). Communication vs. Control: 23.5% vs. 11.8%; adjusted RR (95% CI): 2.12 (1.41 to 3.02). Communication vs. CRP: 23.5% vs. 20.3%; unadjusted RR (95% CI): 0.94 (0.80 to 1.10). Symptom severity score (1-4) 2 to 4 days after consultation: Communication + Combination vs. CRP + Control: 1.84 vs. 1.73; adjusted mean difference: 0.07 (95% CI - 0.03 to 0.16). Communication vs. Control: 1.81 vs. 1.75; adjusted mean difference: 0.06 (95% CI - 0.07 to 0.20). Communication vs. CRP, mean (SD): 1.81 (1.02) vs. 1.70 (1.00) Resolution of symptoms rated 'moderately bad' or worse (median days): Communication + Combination vs. CRP + Control: 6 vs. 5; adjusted HR: 0.83 (95% CI 0.74 to 0.93). Communication vs. Control: 6 vs. 5; adjusted HR: 0.79 (95% CI 0.67 to 0.92). Communication vs. CRP, median (IQR): 6 (3:10) vs. 5 (3:8)

CRP = C-reactive protein, LRTI = lower respiratory tract infection, RCT = randomized controlled trial, RTI = respiratory tract infection, QOL = quality of life, URTI = upper respiratory tract infection

Clinical Interventions

Delayed Prescribing Strategies

Delayed Versus Immediate Prescribing (Usual Care)

Clinic Visits

Four fair-quality RCTs provided moderate-strength evidence that risk of reconsultation within a month was similar for delayed and immediate prescription strategies in adults and children with cough[68,91] and children with sore throat[53] or AOM[41] (Table 15). However, there was low-strength evidence that a delayed prescribing approach may reduce risk of reconsultation within a month in adults with sore throat based on findings from a good-quality prospective cohort study that compared three antibiotic prescribing strategies (immediate, delayed, or no) in 12,829 adults presenting to primary care.[138] Although there is no formal direct statistical comparison between delayed and immediate prescribing strategies, since the magnitude of the reduction in risk of reconsultation is larger for delayed prescribing and the overlap of confidence intervals in minimal, it is possible that delayed prescribing statistically significantly reduces risk of reconsultation compared with immediate prescribing specifically in patients with sore throat.

There was low-strength evidence that at 5 to 6 months after the index visit, reconsultation rates are similar for delayed and immediate prescribing for cough and children with sore throat.[83,91]

Table 15. Reconsultations for delayed compared with immediate antibiotics

Study Design Population and Setting Sample Size	Results
Dowell, 2001[91] RCT Uncomplicated RTI in primary care N = 191	% patients with ≥ 1 reconsultations for similar complaints: Within 1m: 12% vs. 12%; p=0.93 Within total followup (minimum 6 month): 39% vs. 40%; p=0.85
Little, 2005[55,68] RCT Uncomplicated RTI in primary care N = 402	Mean attendances within 1 month: Delayed=0.12 vs. Immediate=0.11; p=NR
Little, 2014[138] Prospective cohort Acute sore throat in primary care N = 11,950	RR (95% CI) of reconsultation within a month, range across models: Immediate vs. no: 0.76 (0.66 to 0.87) to 0.83 (0.73 to 0.94) Delayed vs. no: 0.57 (0.47 to 0.68) to 0.61 (0.50 to 0.74)
Gerber, 1990[83] RCT Children with streptococcal pharyngitis in a private pediatric office N = 113	Unscheduled visits at 5 months: 53% vs. 44%; p=0.18
Pichichero, 1987[53] RCT Children with Group A beta-hemolytic streptococcal pharyngitis in a private pediatric practice N = 114	Reconsultation: 14% vs. 17%, p=0.73[a]
Spiro, 2006[41] RCT Children with AOM in the ED N = 283	Unscheduled visits: 4-6 days: 10% vs. 8%, p=0.70 11-14 days: 15% vs. 11%; p=0.51

[a]Reconsultation rates from Cochrane Review[14] but could not find in primary study publication and time period unknown. EPC calculated p-value.

AOM= acute otitis media, ED = emergency department, NR = not reported, RCT = randomized controlled trial, RTI = respiratory tract infection

Symptoms

Eight RCTs used diverse methods to compare symptomatic improvement between delayed and immediate prescribing strategies (Table 16).[41,53,66,68,72,89,91,117] Among all the findings, however, the most clinically meaningful evidence on patient symptoms comes from two RCTs that assessed duration and rate of moderately bad to severe symptoms that were clearly noticeable to a patient.[68,89] Together, findings from these studies provided low-strength evidence that, compared with immediate antibiotics, a delayed antibiotic strategy increases risk of severe sore throat related symptoms persisting at day 3 and may increase duration of *moderately bad* cough-related symptoms by approximately 1 day.[68] We did not pool data from these two RCTs due to the diversity in clinical presentation (i.e., adults and children with cough as main symptom[68] compared with children with pharyngitis[89]) and outcome assessment (i.e., duration of moderately bad symptoms[68] compared with proportion of patients with severe symptoms[89]). In the RCT of 229 children with pharyngitis seen at pediatric clinics at a University hospital in Jordan between 1988 and 1989, at day 3, delayed prescribing was associated with a higher risk ($p<0.0001$) of sore throat (52% vs. 1%), difficult swallowing (40% vs. 0%), decreased activity (50% vs. 13%), decreased appetite (42% vs. 4%), headache (7% vs. 0%), cervical

lymphadenopathy (40% vs. 1%), irritability (4% vs. 0%), abdominal pain (16% vs. 0%), and vomiting (17% vs. 0%).[89] The RCT that measured duration of moderately bad symptoms used a factorial design to randomize 807 primarily adult patients who presented to primary care clinics in South West England between 1998 to 2003 to no antibiotics, immediate antibiotics, or delayed antibiotics, with or without an information leaflet.[68] Here we only focused on the groups that did not receive the information leaflet. Although this RCT did not directly compare the delayed and immediate prescribing strategies, indirect evidence from their respective comparisons to no antibiotics suggest a longer duration of moderately bad symptoms with delayed antibiotics. Compared with no antibiotics, duration of moderately bad symptoms with delayed antibiotics was similar (mean difference, 0.14; 95% CI, -0.87 to 1.14), but was reduced by 1.08 days with immediate antibiotics (95% CI, -2.1 to -0.09). However, it is unclear what value a 1-day difference in moderately bad symptoms is to patients.

Otherwise, compared with an immediate antibiotic prescribing approach, fever was the only symptom that was consistently statistically significantly worsened by delayed antibiotic prescribing (Table 16).[41,53,66,89,117] However, the clinical importance of the findings were unclear because the differences were marginal in size and of questionable value to the patients (i.e., a day or less in duration, only up to 0.6 degrees Fahrenheit) and they were not accompanied by significant effects on the resolution of various other symptoms.

Table 16. Fever and speed of improvement outcomes for delayed versus immediate antibiotic prescriptions in randomized controlled trials

Study Population Sample Size	Fever	Speed of Any Symptom Improvement
Spiro, 2006[41] AOM N = 238	Total days of fever: 2.3 vs. 1.7; p=0.03	Total days of otalgia: 3.0 vs. 2.7; p=0.35
Little, 2001[72] AOM N = 315	NR	Duration of symptoms in days (all *P*<0.01): Earache: 3.57 vs. 2.56; ear discharge: 1.21 vs. 0.56; night disturbance: 2.35 vs. 1.64; crying: 2.23 vs. 1.54
Arroll, 2002[117] Common cold N = 129	Temperature Fº at Day 10: 96.98 vs. 97.34; p=0.039	NR
Dowell, 2001[91] Cough N = 191	NR	Cough continuing at 13 days: 32% vs. 30% "No difference in duration of other recorded symptoms." (data NR)
Little, 2005[68] Cough N = 269	NR	Duration of symptoms not different between delayed or immediate antibiotics.
Little, 1997[66] Sore throat N = 481	Total days of fever: 2 vs. 1; p=0.04	Median duration in days (all p≥0.39): Sore throat=5 vs. 4; cough=3 vs. 3; headache=2 vs. 2; unwell=3 vs. 4
El-Daher, 1991[89] Sore throat N = 229	Change in temperature, Fº, from Day 1 to 3 (estimated from Figure 2): 101.7 to 100.4 vs. 101.8 to 100.0; p=0.0001	NR
Pichichero, 1987[53] Sore throat N = 114	Change in temperature, Fº, from Day 1 to 3 (estimated from Figure 2): 100.8 to 98.9 vs. 100.5 vs. 98.3; p=0.022	NR

NR = not reported

Satisfaction

We relied on findings from a good-quality Cochrane review meta-analysis for evaluating the comparative satisfaction of delayed versus immediate antibiotics.[14] Results from five RCTs of 1334 adults and children with cold,[117] cough,[68,91] sore throat,[66] or children with AOM provided moderate-strength evidence that up to two weeks after their visit, significantly fewer patients are satisfied or very satisfied with delayed antibiotics (85% vs. 95%; OR 0.52; 95% CI, 0.35 to 0.76).

Return to Work or School

Compared with immediate antibiotics, delaying antibiotics did not statistically significantly increase days missed from work or school in adults with sore throat (median, 1 compared with 2; p=0.13)[66] or in children with AOM (mean, 2.15 compared with 1.97; p=0.56).[72]

Other Treatments

Compared with immediate antibiotics, delaying antibiotics did not statistically significantly increase days of analgesic use in adults with sore throat (4 compared with 3; p=0.46).[66] In children with AOM, delaying antibiotics statistically significantly increased daily number of spoons of paracetamol in the first 3 days after presenting in primary care (2.28 compared with 1.69; p<0.01),[72] but did not increase total days of otic analgesia use (3.2 compared with 3.7; p=0.22) or total days of ibuprofen or acetaminophen (3.2 compared with 2.9; p=0.26) in the 11 to 14 days following ED presentation.[41]

Different Strategies of Delaying Prescriptions

For patients with acute RTIs judged not to need immediate antibiotics, there was low-strength evidence that there are no statistically significant differences between different strategies of delaying prescriptions in duration of moderately bad symptoms, reconsultations, or proportions of patients who were very satisfied with the consultation. This evidence came from a fair-quality RCT of 433 patients seen across 25 primary care practices between March 2010 and March 2012 in the United Kingdom.[70] Giving prescriptions with instructions, leaving prescriptions for collection, postdating prescriptions, or requesting recontact, respectively, led to similar median days of symptoms rated as moderately bad (4 for all), proportions of patients with reconsultations within 1 month (14%, 14%, 10%, 18%; p=0.563) or after 1 month (37%, 32%, 39%, 39%, p=0.391) and proportions of patients who were very satisfied with the consultations (89%, 89%, 80%, 74%, p=0.667). Satisfaction results were available for only 24 percent of the patients.

Outcomes by Subgroups

Some evidence was available to assess variation in reconsultation and satisfaction outcomes based on some subgroup characteristics of interest.

Diagnosis. Type of RTI or setting did not clearly influence the impact of delayed prescribing on reconsultation within the month following the index visit since there was very little variation in the rate difference compared with immediate prescribing for children with AOM seen in the ED (+4%, 11-14 days: 15% vs. 11%; p=0.51),[41] adults and children with uncomplicated RTO seen in primary care in England (0% to +1%, 12% vs. 11% to 12%),[68,91] or children from middle and upper class families with Group A beta-hemolytic streptococcal pharyngitis seen at a private pediatric practice located in suburban Rochester, New York (-3%; 14% vs. 17%, p=0.73).[53]

Clinician Characteristics. For satisfaction, results of the Cochrane review's statistical heterogeneity testing suggested against any clear differences according to variation in patient or clinician characteristics, diagnostic method, or contextual factors for the comparison of delayed versus immediate antibiotics (Chi^2=4.28, df=4, p=0.37; I^2=6%) of delayed versus no antibiotics (Chi^2=0.42, df=2, p=0.81; I^2=0%).[14]

Age. We observed that the strongest effect estimates of satisfaction came from studies of children with AOM compared with studies of adults and children with sore throat, cough, or cold both for the comparison of delayed versus immediate antibiotics and the comparison of delayed versus no antibiotic. Compared with immediate antibiotics, rates of participants who were satisfied or very satisfied were lowest with delayed prescribing in the study of children with AOM (77% vs. 91%, OR 0.32; 95% CI, 0.16 to 0.65).[72] The difference was increasingly smaller in adults and children with cough (82% vs. 90%, EPC pooled OR 0.55; 95% CI, 0.33 to 0.92),[68,91] sore throat (93% vs. 96%; OR 0.61; 95% CI, 0.25 to 1.49),[66] and cold (95% vs. 94%; OR 1.47; 95% CI, 0.32 to 6.85).[117] Likewise, compared with no antibiotics, the strongest increase in satisfaction with delayed antibiotics was in a trial of children with AOM (95% vs. 91%; OR 2.00; 95% CI, 0.65 to 6.18)[101] and was increasingly smaller in trials of adults and children with sore throat (93% vs. 90%; OR 1.49; 95% CI, 0.70 to 3.19)[66] or cough (77% vs. 72%; OR 1.34; 95% CI, 0.84 to 3.19).[68] However, for the comparison of delayed versus no antibiotics, the difference in type of setting between the study of children with AOM and those in adults and children with sore throat or cough (ED versus general practice) may have contributed to the somewhat stronger increase in satisfaction with delayed antibiotics as well.

Delayed Prescribing Versus Clinical Score (Head-to-Head Comparison)

There was low-strength evidence that delayed prescribing leads to an additional day of moderately bad or worse symptoms in patients with sore throat, but does not increase return visits before or after 1 month. This evidence came from a fair-quality RCT of 48 general practitioners and triage practice nurses in general practices in south and central England who saw people ages ≥3 presenting with acute sore throat (2 weeks or less of sore throat) and an abnormal looking throat (e.g. erythema and/or pus) between October 2008 and April 2011.[71] The clinical score used was FeverPAIN, which involved offering immediate antibiotics for score ≥4, delayed antibiotics for scores of 2-3, and no antibiotics for scores of 0-1. The delayed prescription strategy was to leave the prescription for collection after 3-5 days. Duration in days of symptoms rated as moderately bad or worse was 5 for delayed prescribing and 4 for clinical score (HR 1.30; 95% CI, 1.03 to 1.63). There were no differences between the clinical score group and the delayed prescribing group in proportion of patients with return visits within 1 month (8% vs. 8%; RR 0.91; 95% CI, 0.47 to 1.72) or after 1 month (12% vs. 15%; RR 0.79; 95% CI, 0.47 to 1.29).

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing Versus Usual Care

Five fair-quality RCTs that studied point-of-care CRP testing reported on clinical outcomes other than use of antibiotics or medical complications[67,81,93,103-106] (Table 17, Evidence Table 1 [Appendix D]). Relevant outcomes from a single trial were reported in three separate studies.[104-106] The trials assessed a variety of other clinical outcomes, including return clinic visits/reconsultation,[67,81,103-105] improvement in symptoms/speed of improvement,[67,93,103,106] patient satisfaction,[103,105] and use of other diagnostic testing.[106] All interventions targeted clinicians only. Three trials were randomized at the level of the patient[81,93,103] and two were

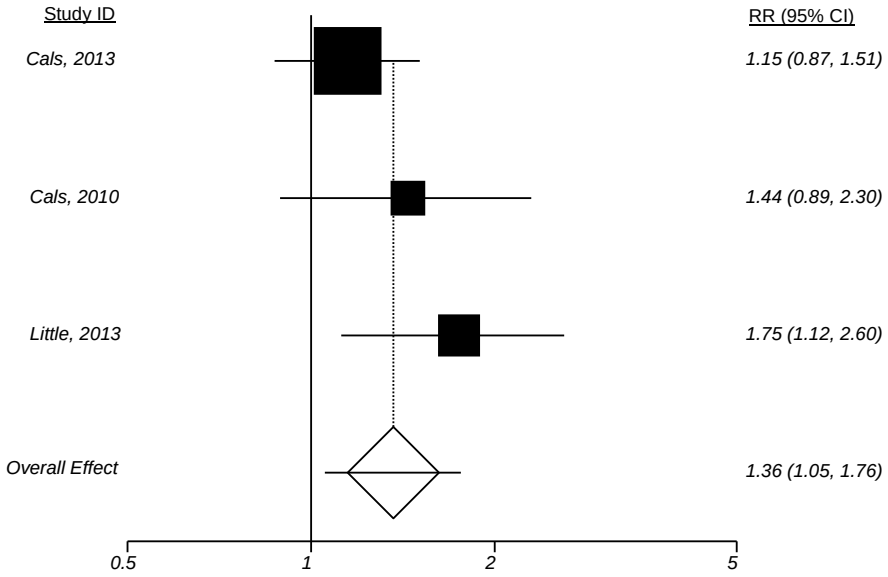
cluster randomized at the level of the clinic or the clinician.[67,104-106] Two trials[67,104-106] were factorial designs that assessed two interventions – one to enhance clinicians' communication skills and one to train clinicians in the use of CRP testing. One trial compared the effectiveness of a clinical algorithm with and without CRP testing as part of the algorithm.[81] The algorithm was used in an urban ED to guide chest x-ray and antibiotic treatment decisions for acute cough illness. All interventions involved some form of in-person training by study personnel. One intervention also included internet-based training and an internal practice-based meeting on prescribing issues.[67]

Return Clinic Visits or Reconsultation

Four trials reported on the outcome of return clinic visits or reconsultation.[67,81,103-105] These studies varied somewhat in their definitions of reconsultation, with one specifying "reconsultation for new or worsening symptoms",[67] one specifying repeat visits for subsequent RTIs during more than 3 years of followup,[104] one specifying subsequent office or ED visits,[81] and two not specifying.[103,105] In a factorial design trial,[67] the reconsultation outcome was part of a composite outcome, "new or worsening symptoms" that included reconsultation for new or worsening symptoms, new signs, or hospital admission, as determined by medical record review. Although reconsultations were not reported separately, 96 percent (730/760) of all patients with data on "new or worsening symptoms" had a reconsultation, with the remaining 4 percent having had hospital admissions. All four studies ascertained reconsultation at 4 weeks[67,81,103,105] and one study at an overall mean of 3.67 years of followup.[104]

Pooling results from three trials that reported reconsultation rates within four weeks of the initial visit, provides low strength evidence that CRP testing increases the risk of reconsultation compared with usual care. The pooled relative risk is 1.36 (95% CI 1.05 to 1.76; $I^2 = 29\%$) (Figure 4).[67,103-105]

Figure 4. Reconsultation with C-reactive protein testing compared with usual care



In a trial predominantly aimed at patients with LRTIs (80%), but including patients with URTI (20%), differences in the relative risk of reconsultation according to LRTI versus URTI[67] between those in the CRP group compared with usual care were not found; URTI adjusted RR 0.99 (95% CI, 0.56 to 1.69) or in those with LRTI adjusted RR 1.04 (95% CI, 0.77 to 1.37), with overlapping confidence intervals.

There was insufficient evidence regarding the effectiveness of CRP testing as part of a clinical algorithm compared with the algorithm alone.[81] A single trial (n=131) found a nonsignificantly higher proportion of return visits in the CRP group: 40 percent (95% CI, 28 to 52) vs. 33 percent (95% CI, 21 to 45), p=0.46. Low strength evidence from one large fair quality trial (n=2119) indicated a borderline significant lower rate of reconsultation in a CRP group compared with a communication training group (20.3% vs. 23.5%; unadjusted RR 0.86; 95% CI, 0.74 to 1.02).[67]

Improvement of Patients Symptoms or Speed of Improvement of Symptoms

There was low strength evidence from four trials of no significant differences between CRP testing and usual care regarding the effect of CRP testing on improvement of patients' symptoms compared with usual care.[67,93,103,106] These studies each used different interventions and assessed improvement of patient symptoms or speed of improvement of symptoms with a variety of outcome measures. They found no significant difference in: proportion of patients feeling recovered on day 7 (23% vs. 25%, p=0.73),[103] mean days off of work (3.35 vs. 3.37),[106] a symptom severity score with a range of 1 – 4 (1.79 vs. 1.79),[67] or median number of days to resolution of symptoms (5 vs. 5; adjusted HR 0.93; 95% CI, 0.83 to 1.04).[67] One study found a higher proportion of patients in the CRP group with "increased or unchanged morbidity" but did not define morbidity (12% vs. 8%; OR 1.6; 95% CI, 1.0 to 2.6).[93]

As with other outcomes, the factorial design trial[67] reported on differences according to LRTI versus URTI. They found a nonsignificantly lower mean symptom severity score for the CRP group compared with usual care in patients with LRTIs (1.72 vs. 1.84; p=0.707) and a nonsignificantly worse mean score for the CRP group in patients with URTI (1.63 vs. 1.44; p=0.186).[67] While no difference was found in the time to resolution of moderately bad symptoms among the CRP group compared with the usual care group overall, a small nonsignificant increase in time to resolution was found in patients with URTI (4 vs. 3.5; adjusted HR 0.81; 95% CI, 0.59 to 1.11). In the subgroup with LRTI, the difference in median days to resolution between CRP group and usual care was the same as in the overall group (5 vs. 5; adjusted HR 0.89; 95% CI, 0.77 to 1.07). Another trial reported on the proportion of patients feeling recovered on day 7 according to type of RTI: LRTI and rhinosinusitis.[103] The study found that among patients with LRTIs a nonsignificantly higher proportion in the CRP group felt recovered at day 7 compared with usual care (23.5% vs. 18.4%, p=0.53) whereas among patients with rhinosinusitis a nonsignificantly lower proportion in the CRP group felt recovered (22.4% vs. 28.9%, p=0.37).

Patient Satisfaction

Evidence from two trials was insufficient to draw conclusions regarding the effect of CRP testing on patient satisfaction compared with usual care.[103,105] The first study (n=431) reported on the proportion of patients who were at least "very satisfied" and found no difference between the CRP group and usual care (77% vs. 76%; unadjusted RR 1.01; 95% CI, 0.91 to 1.13).[105] The second study (n=258) also assessed the proportions of patients who were at least "very satisfied"

and found a higher patient satisfaction the CRP group (76.3% vs. 63.2%; unadjusted RR 1.21; 95% CI, 1.02 to 1.43).[103]

Use of Other Diagnostic Tests

One trial (n=431) provided insufficient information to assess the strength of evidence regarding the effect of CRP testing on the use of other diagnostic testing compared with either usual care or with communication skills training.[106] The study reported on a small number of events and found no significant differences between the CRP group and usual care in the use of: chest x-ray (5% vs. 7%), blood testing (1% vs. 0%), or other tests such as spirometry or sputum analysis (2% vs. 2%). It also found no significant differences between the CRP group and communication skills training for the same outcomes: chest x-ray (5% vs. 5%), blood testing (1% vs. 1%), and other tests (2% vs. 0%).

Table 17. C-reactive protein point-of-care testing interventions: Key Question 4 outcomes

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Cals, 2009[105] Practice N = 20 Provider N = 40 Patient N = 431 Adults; suspected LRTI and cough < 4 weeks Fair quality	2 X 2 factorial cluster RCT (clinic level). September 2005 - March 2006 and September 2006 - March 2007. Followup: 28 days.	Intervention: *Communication skills training*: based on 11 key tasks (e.g., exploring patient's fears and expectations, asking patient's opinion of antibiotics), and elicit-provide-elicit framework. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual Care	Communication + Combination vs. CRP + Control: Reconsultation within 28 days: 34.8% vs. 30.4%; unadjusted RR 1.15, 95% CI 0.87 to 1.51; p=0.50 (p-value from model adjusted for practice level). Patient satisfaction (% at least very satisfied): 76.8% vs. 76.0%; unadjusted RR 1.01, 95% CI 0.91 to 1.13; p=0.53 (p-value from model adjusted for practice level).
Cals, 2010[103] Practice N = 11 Provider N = 33 Patient N = 258 Adults ≥18 y; first consultation for LRTI or rhinosinusitis Fair quality	RCT (individual level). November 2007- April 2008. Followup: 28 days	Intervention: CRP testing during consultation. Clinicians advised to combine CRP results with clinical findings. Control: usual care (immediate, delayed, or no antibiotics).	Reconsultation: 25.6% vs. 17.8, unadjusted RR 1.44, 95% CI, 0.89 to 2.30; p=0.13. Patient feels recovered on day 7: Overall: 22.9% vs. 24.8%, p=0.73. Rhinosinusitis: 22.4% vs. 28.9%, p=0.37 LRTI: 23.5% vs. 18.4%, p=0.53 Patient satisfaction (≥ very satisfied): 76.3% vs. 63.2%, unadjusted RR 1.21, 95% CI, 1.02 to 1.43; p=0.02.
Cals, 2011[106] (see Cals, 2009[105])	See Cals, 2009[105]	See Cals, 2009[105] (above)	Days off of work, days (SD): Communication vs. Control: 3.35 (4.54) vs. 3.37 (3.77) Communication vs. CRP: 3.35 (4.54) vs. 3.37 (4.02) Use of other diagnostic testing: Chest x-ray: Communication vs. Control:: 5% vs. 7% Communication vs. CRP: 5% vs. 5% Blood tests: Communication vs. Control: 1% vs. 0% Communication vs. CRP: 1% vs. 1% Other (spirometry, sputum): Communication vs. Control: 2% vs. 2% Communication vs. CRP: 2% vs. 0%

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Cals, 2013[104] (see Cals, 2009[105]) Patient, N = 379	See Cals, 2009[105]	See Cals, 2009[105] (above)	Communication + Combination vs. CRP + Control: Office visits for RTIs during followup (mean overall followup of 3.67 years), Mean No. per patient per year (95% CI): 0.40 (0.33 to 0.47) vs. 0.56 (0.43 to 0.68), p=0.12 (p-value from model adjusted for practice level).
Diederichsen, 2000[93] Practice N = 35 Provider N = 35 Patient N = 812 Adults and children with RTI Fair quality	RCT (individual level). January 1997- April 1997. Followup: 7 days	Intervention: CRP testing during consultation. Control: usual care (clinical assessment only).	Increased or unchanged morbidity* after 1 week: 12% vs. 8%, adjusted** OR 1.6, 95% CI, 1.0 to 2.6; p=0.05.
Gonzales, 2011[81] Practice N = 1 Provider N = NR Patients N = 131 Adults ≥ 18 y; cough ≤ 21 days and one other acute RTI symptom Fair quality	RCT (individual level). November 2005 – March 2006. Followup: 2 to 4 weeks	Interventions: *CRP testing + algorithm:* CRP testing and clinical management algorithm to guide chest x-ray and antibiotic treatment decisions. *Algorithm only:* Clinical management algorithm (without CRP testing) to guide chest x-ray and antibiotic treatment decisions.	Return visits (office or ED): 40% (95% CI, 28% to 52%) vs. 33% (95% CI, 21% to 45%), p=0.46.
Little, 2013[67] Practice N = 228 Provider N = 372 Patient N = 4,121 Patients > 18 y; acute RTI (upper or lower) Fair quality	2 X 2 factorial cluster RCT (clinic level). February 2011 – May 2011. Followup: 4 weeks	Interventions: *Communication skills training*: Internet-based training in communication skills; interactive booklet; video demonstrations. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual care.	Reconsultation for new or worsening symptoms within 4 weeks (composite outcome including hospital admissions, of which 3.9% (30/760) overall was hospital admission): Communication + Combination vs. CRP + Control: 18.5% vs. 18.4%; adjusted RR (95% CI): 1.05 (0.78 to 1.39). Communication vs. Control: 20.3% vs. 11.8%; adjusted RR (95% CI): 1.75 (1.12 to 2.60). Communication vs. CRP: 20.3% vs. 23.5%; unadjusted RR (95% CI): 0.86 (0.74 to 1.02). Symptom severity score (1-4) 2 to 4 days after consultation, mean : Communication + Combination vs. CRP + Control: 1.79 vs. 1.79; adjusted mean difference: 0.0 (95% CI - 0.09-0.09). Communication vs. Control: 1.70 vs. 1.75; adjusted mean difference: 0.01 (95% CI - 0.12 to 0.15). Communication vs. CRP, mean (SD): 1.70 (1.00) vs. 1.81 (1.02) Resolution of symptoms rated 'moderately bad' or worse (median days): Communication + Combination vs. CRP + Control: 5 vs. 5; adjusted HR: 0.93 (95% CI, 0.83 to 1.04). Communication vs. Control: 5 vs. 5; adjusted HR: 0.74 (95% CI, 0.74 to 1.03). Communication vs. CRP, median (IQR): 5 (3, 8) vs. 6 (3, 10)

* Morbidity was not otherwise defined. ** Specific variables adjusted for were not specified.
CRP = C-reactive protein, ED = emergency department, LRTC = lower respiratory tract infection, RCT = randomized controlled trial, RTI = respiratory tract infection

Procalcitonin Point-of-Care Testing

A good quality systematic review provides low strength evidence that use of procalcitonin algorithms in the primary care setting to help identify appropriate adult patients for antibiotic treatment did not significantly affect the medium number of days with limited activity (9 days in both groups), number of days missed from work (4.9 and 4.8 days), and numbers of patients with continuing or relapsed symptoms at 28 days (30% in each) compared with usual care.

In the ED setting, no difference was found in quality of life or patient assessment of illness burden. Along with other factors, this evidence is considered insufficient because these results combine patients with CAP, exacerbations of chronic obstructive pulmonary disease and acute bronchitis.

Tympanometry Point-of-Care Testing

In a fair quality RCT of providing physicians with results of tympanometry for children ages 3 to 36 months with suspected AOM, there was no difference between tympanometric curves (normal bilaterally, some movement bilaterally, and flat curve on either side) between groups for children who were prescribed an antibiotic (p-values 0.84, 0.14, and 0.10, respectively).[42] This evidence was indirect for measuring symptom differences between groups, and insufficient for drawing conclusions.

Viral and S. pneumococcal (Rapid Strep Tests) Point-of-Care Testing

No evidence was found for viral and S. pneumococcal point-of-care testing.

System-Level Interventions

Three fair quality trials of electronic clinical decisionmaking tools provide low-strength evidence of no impact on reported healthcare utilization compared with usual care. Two studies reporting ED visits within 30 days found no differences between decision support and control groups. Rates were low in both studies, for example one study of patients with pharyngitis or respiratory infection reported 0.7 percent in the intervention group and 0.5 percent in the control group (p=0.99).[59] Further, return outpatient clinical visits were similar for intervention and control groups (7.7% intervention and 11.3% control). In a study of patients with acute bronchitis, ED visits within 30 days were rare across all sites and periods (usual care, paper-based and electronic decision support; baseline and postintervention), with between 0 to 0.1 of percent patients returning across intervention or control sites.[80] Similarly, in a study of patients with acute RTI, the proportion of patients who returned within 30 days for an additional physician visit (reconsultation) was similar between intervention and control arms of their study (23% intervention and 26% control, p=0.32).[73]

Multifaceted Interventions

Five trials and three observational studies reported on clinical outcomes other than use of antibiotics or medical complications.[4,34,55,60,64,68,120,132]

Patient Satisfaction

Two studies involving multiple interventions for clinicians (e.g., education, practice profiling, academic detailing) and patient education programs provide low-strength evidence of no impact on patient satisfaction.[34,132] In a fair-quality trial conducted in the Netherlands,[34] provider group education, prescribing feedback, and patient educational material did not affect the degree of patient satisfaction despite a reduction in prescribing rates (0% vs. 0% change).

Patient satisfaction was also measured in a US study in patients seen in study and control clinics for acute bronchitis 1 year after the intervention (patient education and a physician-centered quality improvement project involving education, practice profiling, and academic detailing) and found no difference in the degree of satisfaction in a combined intervention (63% vs. 69%, p=0.15, adjusted RR 1.1; 95% CI, 0.81 to 1.3).[132]

Two US studies,[60,120] evaluated the relationship between receipt of an antibiotic prescription and patient satisfaction in studies with interventions aimed at patients only. One study used a combined educational and communication intervention and found all dimensions of satisfaction were higher when an antibiotic was not prescribed (3.74 vs. 4.22; p=0.005). [120] The other study compared parents of children with AOM who received an educational intervention and watchful waiting or immediate antibiotics. Parent satisfaction was the same between groups regardless of treatment (total satisfaction score 45 for both groups).[60] This evidence is insufficient due to lack of consistency and sparseness.

Reconsultation

Two studies that evaluated how adding an information leaflet to delayed prescribing affects reconsultation had mixed results.[55,64,68] Two fair quality US trials conducted in the same population used consultation behavior as a measure of the impact of the intervention on overall clinic visits.[55,68] In these trials, providing an information leaflet to patients as an adjunct to the use of a delayed prescription strategy led to a small but statistically significant increase in reconsultation within 1 month of initial consultation (17% vs. 1%; p=0.02). However, the rate of clinic attendance for cough within 1 month to 1 year after seeing a doctor was not different between groups. A fair-quality trial from the UK showed no difference in consultation rates in the next month among patients randomized to receive an informational leaflet or not in addition to receiving an antibiotic prescription with advice to fill if symptoms worsened (10.6% vs. 13.3%).[64] Because of the inconsistency in these findings, this evidence is insufficient to draw a conclusion.

No difference in return visits in 30 days for patients with acute bronchitis or pneumonia between intervention versus control groups was found in a large fair quality observational US study trial involved patient education and a physician-centered quality improvement project (education, practice profiling, and academic detailing).[4] This evidence is insufficient to draw conclusions on the impact of combined patient and provider education on return office visits.

Point-of-Care Tests Combined With Other Strategies

CRP Combined With Provider-Focused Communication Training

Symptoms

There was low-strength evidence that the combination of internet-based CRP plus enhanced communication training extends the median number of days of moderately bad symptoms compared with the control group, but not compared with use of CRP or communication training alone.[67] This evidence came from the GRACE consortium-supported trial described above which found that the median number of days of moderately bad symptoms was 5 in the control and CRP alone groups and 6 in the communication alone and combination groups.[67] The adjusted hazard ratios for the control group compared with each of the intervention groups was 0.87 (95% CI, 0.74 to 1.03) for the CRP alone group, 0.79 (95% CI, 0.67 to 0.92) for the communication training group, and 0.77 (95% CI, 0.65 to 0.91) for the combination group. Although the

intervention groups were not directly compared with one another, it is likely they have comparable effects on resolution of moderately bad symptoms as their effects compared with the control group all indicate an increase of similar magnitude and there is considerable overlap in their confidence intervals. Although the IMPAC^{3}T trial reported that symptom scores were similar for all groups, the clinical relevance of this finding is unclear in the absence of the supporting data and information about severity.[106]

Reconsultation, Diagnostic Testing Use, Days Off Work

There was low-strength evidence that use of the combined intervention of small-group face-to-face communication training plus use of CRP testing leads to similar reconsultation rates, diagnostic testing use and days off work compared with communication training alone, CRP testing use alone and usual care.[106] These findings came from the IMPAC^{3}T trial described above.[105] Individual group results were provided (Table 18), but results of statistical testing of between-group differences were not reported. Authors noted that reconsultation rates and patient-reported time to recovery were similar for all groups, but did not comment on the comparability of the diagnostic testing usage.

Table 18. Key Question 4: Outcomes for communication training combined with CRP testing in Cals, 2011[106]

Outcome	CRP Alone (N=110)	Communication Training Alone (N=84)	Communication Training Plus CRP (N=117)	Usual Care (N=120)
Mean days off work	3.35	3.37	3.39	3.37
Average reconsultations	0.40	0.18	0.27	0.37
Chest x-ray	0.05	0.05	0.09	0.07
Blood	0.01	0.01	0.05	0.00
Other (spirometry, sputum)	0.02	0.00	0.02	0.02

CRP = C-reactive protein

Rapid Streptococcal Antigen Detection Test Added to a Decision Rule

There was low-strength evidence that the combination of a rapid streptococcal antigen detection test plus a decision rule has comparable effects on symptom improvement and return visits compared with use of the clinical score alone or delayed prescribing. This evidence came from an RCT that involved 48 general practitioners and triage practice nurses in general practices in south and central England who saw people ages ≥3 presenting with acute sore throat (2 weeks or less of sore throat) and an abnormal looking throat (e.g., erythema and/or pus) between October 2008 and April 2011.[71] The clinical score used was FeverPAIN, which involved offering immediate antibiotics for score ≥4, delayed antibiotics for scores of 2-3, and no antibiotics for scores of 0-1. There were no statistically significant differences between the combination of the rapid streptococcal antigen detection test plus a decision rule, the decision rule alone, or delayed prescribing in duration in days of moderately bad or worse symptoms (4 vs. 4 vs. 5) or in proportion of patients who returned within 1 month (6%, 8%, 8%) or after 1 month (16%, 12%, 15%).

Key Question 5. For patients with an acute respiratory tract infection and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on achieving intended intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute respiratory tract infections (clinicians and/or patients), improved shared decisionmaking regarding the use of antibiotics, and improved clinician skills for appropriate antibiotic use (e.g., communication appropriate for patients' literacy level and/or cultural background)?

Key Points

Educational Interventions

- Low-strength evidence suggested that knowledge is improved in the short-term with clinic-based interventions but evidence was more mixed for community-based interventions with longer-term followup.
- Evidence on the impact of educational interventions for patients (or parents) on expectations or attitudes towards antibiotic use for acute RTIs was insufficient due to inconsistency of findings across studies.

Communication Interventions

- Studies have not found a reliable association between interventions to improve clinician-patient communication regarding antibiotic use for acute RTIs and any intended intermediate outcomes.

C-Reactive Protein Point-of-Care Testing

- A single study did not find a reliable association between point-of-care CRP testing and either of two intermediate outcomes compared with usual care.

Detailed Assessment

Educational Interventions

Seven RCTs (3 group or cluster randomized),[45,79,85,95,102,114,120] one non-RCT,[51] and six observational (pre-post) studies[134,144,147,157,160,161] evaluated gains in knowledge and changes in attitude of patients regarding use of antibiotics for acute RTI following education interventions. These were mostly fair-quality studies and broken down into three main groups by intervention methods. The first group was studies that used clinic-based passive interventions, pamphlets with or without waiting room posters.[51,85,120,144] Also considered with this group were two studies of video-based interventions[114,160] and one that compared video and pamphlet interventions to each other.[45] The second group was five studies of community or national campaigns, mostly using public campaigns, but not exclusively.[79,134,147,157,161] Finally there were two studies of unique interventions, one assessing preference for variations in the graphical format of information presented[102] and the other an active education program aimed at child care services workers and measuring change in parent knowledge about acute RTIs.[95] Outcomes assessed in these studies varied from surveys assessing patient or parent knowledge about when it is appropriate to use

antibiotics to assessing attitudes and expectations for receiving antibiotic treatment for an acute RTI. These outcomes were considered separately, although they likely overlapped.

Overall, the evidence suggested that knowledge is improved in the short term with clinic-based interventions but evidence is more mixed for community-based interventions with longer-term followup. For example, a good-quality cluster RCT found temporal trends for improvement in knowledge in both groups studied.

Evidence on the impact of educational interventions for patients (or parents) on expectations or attitudes towards antibiotic use for acute RTIs was insufficient due to inconsistency of findings across studies. No clear patterns based on population target (adult, child, all), intervention type (clinic-based vs. population-based and specific tools used), study size, or type and number of questions asked emerged. The clearest groupings are based on study design and duration. Three of five trials suggested no difference between groups while all four pre-post observational studies found changes in expectations and attitudes. A potential explanation for this difference is temporal trends in changes in attitudes towards antibiotics over time in the general population. Clinic-based studies are typically fairly short duration, and four of six found a benefit with the intervention. In contrast two pre-post studies of longer duration public education campaigns (2-4 years) found a benefit over time, while a cluster RCT of a community-based intervention did not. Among studies that found a benefit, there was inconsistency in the magnitude of change and the meaning of specific differences between groups is unclear.

Knowledge

Evidence suggested that video-based interventions improve knowledge among urban parents, but not in the overall population targeted. A study using a 20-minute video plus a pamphlet found no difference in knowledge scores 2 months postintervention, although the subgroup of patients from urban clinics was significantly improved after the video (mean 6.02 vs. 6.92 out of 11; $p=0.003$).[114] The other study of a 3-minute animated video viewed in an urban ED found significant improvements in score immediately after the video (median 9 vs. 10 out of 10; $p<0.001$), and this improvement was maintained at 4 weeks.[45] The control group remained the same throughout (8 points) and a pamphlet group improved by 2 points immediately after the intervention (from 8 to 10 out of 10) and decreased by one point at 4 weeks.

Knowledge about appropriate use of antibiotics, including use for acute RTIs, following national or community-wide campaigns were evaluated in one good-quality cluster RCT[79] and two observational studies.[147,157] Findings from these studies suggest that the interventions did not improve parent knowledge about appropriate antibiotics use in acute RTIs. The best evidence came from a cluster RCT involved 16 communities in Massachusetts, matched for size, demographics, and other factors. The intervention (six newsletters aligned with cold and flu season over 3 years, as well as pamphlets, posters, stickers, etc. in clinic waiting rooms) was aimed at parents. Pre and postsurvey scores improved in both groups and there were no differences in the proportion answering 7 of 10 questions correctly (adjusted OR 1.2; 95% CI, 0.8 to 1.7) or mean improvement in score (0.1; 95% CI, -0.2 to 0.4). Regression analyses indicated that parents who had more education, were older, were white, were a stay-at-home parent, were not receiving Medicaid, and whose child was over 12 months had significantly higher odds of answering 7 or more questions correctly.

A nonrandomized prospective study of communities in Wisconsin distributed the CDC's pamphlet on antibiotic use in children, followed by nurse-led education sessions for parents at schools and day care centers.[157] Based on a four-question survey regarding awareness of the risk

for antibiotic resistance, the study found that more parents in the intervention group agreed with the statements than the control group (difference 10%; 95% CI, 1.9 to 18.1). Regarding appropriateness of antibiotics, both groups improved responses for colds, flu, and dry cough; neither improved for bronchitis; and only the intervention group improved for nonstreptococcal sore throat. Lastly, the study of a national campaign in England described fully in Key Question 1 evaluated general knowledge of antibiotic use and misuse and found no differences between intervention an control groups on 9 of 10 questions; a question on keeping leftover antibiotics for future use showed better improvement in the control group.[147]

A study designed to educate day care workers as a method of improving parent knowledge and attitudes towards antibiotic use found that their enrolled populations varied by the proportion with/without a college education/significantly.[95] Stratified analyses showed improved scores in the college-intervention group compared with control on overall knowledge scores (0.5 point difference on 9-point score; $p<0.01$), while the group without a college education showed no difference between groups. Multivariate analysis indicated that parent characteristics of being white and having a college degree were associated with a high knowledge score ($p=0.02$ for each). This evidence is insufficient to draw conclusions about this intervention.

Expectations, Attitudes, Beliefs

Clinic-based interventions (videotapes, pamphlets, and posters) were mostly aimed at parents of young children. Two small trials found no impact[114,120] while a larger cluster RCT, a non-RCT (aimed at young adults), and two observational studies found that the intervention groups improved in responses to surveys of expectation for antibiotics, attitudes or beliefs towards using antibiotics, or anticipated behavior regarding use of antibiotics for acute RTIs.[51,85,144,160]

In studies of public campaigns, two pre-post studies of national campaigns that relied mainly on public campaigns reported improvement in attitudes and expectations of adults surveyed.[134,161] A study in Israel, with exposure over 4 winter months in 2 consecutive years, found that parent level of agreement with statements about appropriate antibiotic use and risks of overuse improved significantly ($F=4.18$, $p=0.04$). Further, analysis by sex of parent indicated that female parents showed more improvement than males ($p=0.001$). In a similar 4-year study in Australia (exposure to intervention over 3 winter months), adults were surveyed annually for 3 years about their beliefs regarding use of antibiotics for cough, colds, and flu. The study reported a decrease in the number who believes that taking antibiotics for colds and flu is appropriate (-7%, 95% CI, 3.5 to 10.5). In contrast, a cluster RCT of 16 communities in Massachusetts, matched for size, demographics, and other factors found no difference between intervention and control communities in parents' expectation for antibiotics, based on three questions that included issues of satisfaction and intent to change providers.[79] The intervention (6 newsletters aligned with cold and flu season over 3 years, as well as pamphlets, posters, stickers, etc. in clinic waiting rooms) was aimed at parents.

Finally, a unique study from Norway evaluated response to varying visual displays of information about appropriate use of antibiotics for acute RTIs using a Web interface and found that compared with receiving no information, face icons and bar graphs did not lead to more subjects responding that they would not go to the doctor for a sore throat with 3 days of symptoms.[102] In fact, bar graphs and face icons of the percentage of patients with symptoms at 3 days with and without antibiotics had worse outcomes. Responses improved after subjects read detailed educational material, but even then the percent that would choose to visit the doctor at 3 was lowest in the no-visual information group.

Communication Interventions

Of the seven trials that studied interventions to improve communication between clinicians and patients regarding the use of antibiotics for acute RTIs (Evidence Table 1 [Appendix D]), five fair-quality studies reported on various intermediate outcomes.[75,76,105,110,120] In most cases, the intermediate outcomes studied were rooted in or directly related to the theoretical model underlying the intervention and were explicitly intended outcomes of that intervention.

Two trials reported on patient enablement, self-efficacy, and intention to consult for similar illness in the future, with no significant difference found. One trial aimed at parents of children being seen in clinic for an acute RTI used an intervention based on Social Cognitive Theory.[120] This study assessed parents' self-efficacy to communicate with their child's clinician, a construct based on Social Cognitive Theory that the intervention was design to improve. The trial was a factorial design study that found parents who received the communication intervention had higher scores than those who did not receive the communication intervention (93.47 vs. 86.28, respectively; p=0.021). In contrast, in a trial reporting on a "patient enablement score" that was not was not explicitly described or placed within a theoretical framework, the mean patient enablement score (scale 0-12) there was no significant difference between groups scores (8.49 vs. 8.15; adjusted difference: 0.35; 95% CI, -0.05-0.75).[110] A second study reported on "patient enablement" using a scale with a maximum score of "12",[105] but it is not clear that the two studies used the same measure. The second study also found a no significant difference in scores between the communication intervention compared with usual care, but the absolute scores were much lower (3.29 vs. 3.06; difference: 0.23; p=0.70 from an adjusted model). The same study reported on "patients' intention to consult for similar symptoms in the future", and found a lower proportion of the communication intervention group intended to consult in the future compared with usual care, although not reaching statistical significance (73.6% vs. 80.1%; p=0.16 from an adjusted model).[105]

Two trials studied interventions specifically designed to improve shared decisionmaking (Table 19), an approach in which the values, preferences and opinions of both the patient and the clinician are made explicit and considered in the decision.[75,76] The second of these shared decisionmaking trials[76] studied a revised version of the intervention used in the first trial.[75] Each trial assessed a variety of intended intermediate outcomes related to shared decisionmaking. Both studies used the Decisional Conflict Scale (scale: 1=low conflict; 5=high conflict) among patients and clinicians to assess the level of conflict the clinician or patient felt. One study reported a weak positive correlation between patient and clinician responses to the Decisional Conflict Scale (Pearson's r=0.26; p=0.06).[75] The other study compared the mean proportions of scores ≥2.5 in the intervention and control groups, reported for patients and clinicians separately.[76] There was no significant difference in the risk of decisional conflict for clinicians or patients in the interventions group compared with the control group, although the estimates were very imprecise and the point estimates were inconsistent (Table 19). Similarly, neither study found any large or statistically significant difference between an intervention group and a control group (patients or clinicians) in perceived quality of the decision (scale 1-10).[75,76] Using the Decision Regret Scale (scale 1-100), one study reported no difference in the proportion of patients with decisional regret in the intervention group compared with the control group (7% vs. 9%, respectively; p=0.91)[75] and the other study reported a slightly higher mean score in the intervention patients compared with the control patients (12.4 vs. 7.6; adjusted mean difference 4.8; 95% CI, 0.9 to 8.7).[76] This study assessed patients' adherence to their decision 2 weeks after the clinic visit and found no significant difference between intervention and control groups.[76]

The same study assessed patient perceptions of how much they had participated in decisionmaking during the consultation and found that a higher proportion of patients in the intervention group compared with the control group reported having an active role in the decisionmaking process (67% vs. 49%).[76]

Both shared decisionmaking studies also assessed the intention of patients and clinicians to engage in shared decisionmaking in future consultations regarding the use of antibiotics for acute RTIs. Again, neither study found any large or statistically significant difference between an intervention group and a control group (patients or clinicians) in the intention to engage in shared decisionmaking in future consultations.[75,76] Finally, both studies reported on an intermediate outcome not directly related to shared decisionmaking, which was clinicians' intention to follow clinical practice guidelines regarding prescribing antibiotics for acute RTIs. Neither study found a large or statistically significant difference between an intervention group and a control group.[75,76]

Table 19. Intermediate outcomes with interventions to improve communication between clinicians and patients

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Légaré, 2010[75] Practice N = 4 Provider N = 33 Patient N = 459 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2007 – March 2008 Followup: 2 weeks	Intervention: Interactive workshops on URTIs, risk communication, fostering patient participation in decisionmaking, shared decisionmaking support tools. Control: Delayed intervention.	Difference (95% CI) Correlation of clinician and patient Decisional Conflict Scale (Pearson's *r*): 0.26 (-0.06 to 0.53), p=0.06. Quality of decision, mean score (1-10): Clinicians: 0.2 (-0.34 to 0.89), p=0.29; Patients: 0.1 (-0.88 to 0.94), p=0.57. Patients with decisional regret (%): -2 (-12 to 5), p=0.91. Intention to engage in shared decisionmaking, mean score (-3 to +3): Clinicians: 0.5 (-0.2 to 1.3), p=0.77; Patients: -0.1 (-0.6 to 0.4), p=0.16. Intention of clinicians to comply with clinical practice guidelines, mean score (-3 to +3): -0.1 (-0.7 to 0.5), p=0.58.
Légaré, 2012[76] Practice N = 9 Provider N = 149 Patient N = 359 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2010 – April 2011 Followup: 2 weeks	Intervention: 2-hour online tutorial and 2-hour onsite interactive workshop on decisionmaking about antibiotic treatment for RTIs and communication with patients. Control: Usual care.	Decisional Conflict Scale (% with score ≥ 2.5), adjusted RR (95% CI): Patients: 0.8 (0.2 to 2.4); Clinicians: 3.4 (0.3 to 38.0). Quality of decision (scale 1-10), mean difference (95% CI): Patients: 0.0 (-0.4 to 0.4); Clinicians: -0.2 (-0.6 to 0.2). Intent to engage in shared decisionmaking (scale -3 to +3), mean difference (95% CI): Patients: 0.2 (-0 to 0.4); Clinicians: 0.0 (95% CI -0.3 to 0.2). Patient adherence to decision (%): adjusted RR (95% CI): 1.0 (0.9 to 1.0). Patient regret over decision (scale 1-100), mean difference (95% CI): 4.8 (0.9 to 8.7). Intention of clinicians to comply with clinical practice guidelines, (scale -3 to +3), mean difference (95% CI): -0.2 (-0.5 to 0.1).

RCT = randomized controlled trial, RTI = respiratory tract infection

Clinical Interventions

Delayed Prescribing Strategies

No evidence was found for delayed prescribing strategies.

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

One fair-quality trial of point-of-care CRP testing reported on various intermediate outcomes[105] (Evidence Table 1 [Appendix D]). The study was of a factorial design that assessed two interventions – one to train clinicians in the use of CRP testing and one to enhance clinicians' communication skills regarding antibiotic use for acute RTIs. This study assessed two intermediate outcomes, neither of which was directly related to any theoretical model underlying the use of CRP testing to guide decisions about antibiotic use for acute RTIs. The study reported on "patients' intention to consult for similar symptoms in the future", and found that a nonsignificantly lower proportion of the CRP testing group intended to consult in the future compared with usual care (75.4% vs. 78.9%; p=0.52 from model adjusted for communication skills training). The study also reported on "patient enablement" using a scale with a maximum score of "12", and found a nonsignificantly lower score in the CRP testing group (2.97 vs. 3.40, p=0.13 from model adjusted for communication skills training).[105]

Other Point-of-Care Tests (Procalcitonin, Viral, Rapid Strep)

No evidence was found for other point-of-care tests.

System-Level Interventions

No evidence was found for system-level interventions.

Multifaceted Interventions

No evidence was found for multifaceted interventions.

Key Question 6. What are the comparative nonclinical adverse effects of strategies for improving the appropriate use of antibiotics for acute respiratory tract infections (e.g., increased time burden on clinicians, patients, clinic staff)?

Key Points

- Evidence was insufficient to draw conclusions about the nonclinical adverse effects of interventions to improve appropriate antibiotic prescribing.
- The estimates of the time burden associated with interventions ranged from a few minutes with several interventions to more than 10 hours and only one study actively measured time burden for clinicians to take an online training for CRP testing, communication skills, or both and found the combination to require up to 13 minutes longer. There are no estimates on the time and other resources needed to develop and deploy the interventions within a clinic or health system.

Detailed Assessment

Educational Interventions

No study of educational interventions explicitly measured adverse consequences of creating and implementing the intervention, although some discussed related issues such as lack of participation in the education program by some clinicians, or patient participants stopping the education program part way through. A few studies described the amount of time interventions required of the participants, but very few addressed the time needed for development of the educational materials. Of the studies reporting the time required for clinicians participating in educational sessions, seven were 1 to 5 hours in duration[32,56,63,77,88,100,133] and two were 1 and 2-day sessions.[49,150] There was no assessment of whether or when such sessions might need to be repeated.

For patient education, intervention times were generally kept purposefully short. Video interventions lasted 3 to 20 minutes[39,45,114,160] depending on whether they were intended to be viewed in the clinic or at home. Time required for reading educational pamphlets were reported only in two studies, reported as 5 to 15 minutes.[45,135] An interactive computer kiosk educational program took patients 9 to 45 minutes complete. Finally, child care workers were given 45-minute presentations but the time each of these participants spent subsequently educating parents was not recorded.[95,133]

Communication Interventions

None of the seven trials of interventions to improve communication between clinicians and patients explicitly measured adverse consequences of creating and implementing the intervention, although some discussed related issues such as lack of participation by some clinicians. Six trials described the amount of time the various interventions required of the participants.[67,75,76,105,110,120] Five of the trials targeted clinicians, four of which had interventions requiring between 4 hours and 10 hours of participant time:[75,76,105,110]

- Combined communication and educational intervention about prescribing guidelines required a combined total of 10 hours.[110]
- Seminars and practice with simulated patients requiring a total of 4 hours.[105]
- Three 3-hour interactive workshops on shared decisionmaking, for a total of 9 hours.[75]
- A two-hour online tutorial and a two-hour on-site interactive workshop, for a total of 4 hours.[76]

In contrast, a trial using an internet-based training module reported a mean time of 37.4 minutes for training.[67] This study reported that 87.0 percent of clinicians completed the communication skills training.[67] The single trial that targeted the parents of pediatric patients required seven minutes of participant time.[120]

Although these are real concerns for the feasibility of such communication training interventions, at least one trial recognized the potential counter-balancing benefit of providing continuing medical education credit for participating clinicians.[75] Another trial found that the effect of communication training on antibiotic prescribing may extend for several years, suggesting that a long-term benefit of such interventions may counter balance the time required up front.[104] In this followup study of a previously reported trial,[105] clinicians who received the communication intervention were less likely to prescribe antibiotics for subsequent acute RTIs during a mean overall followup time of 3.67 years after the intervention (26.3% vs. 39.1%;

p=0.02). Conversely, the single poor-quality trial found that the rate of antibiotic prescription among clinicians who received communication training, which decreased at 6 weeks after the intervention (from 36.4% to 29.4%), was back to the baseline rate at 12 months of followup (36.7%).

Clinical Interventions

Delayed Prescribing Strategies

The studies of clinical strategies did not specifically measure or report on increased time burden on clinicians, sustainability of intervention (e.g., adherence to algorithm), or measures of resource use associated with ordering and interpreting the test. Compared with issuing an immediate antibiotic prescription, conceivably there is at least some increase in time burden for clinicians using delayed prescribing strategies in (1) getting oriented to using a new prescribing approach, (2) explaining to patients the likely natural history of their illness and that it would probably not be helped by antibiotics, (3) providing instructions on how to decide if and when to use the prescription, and (4) fielding patients' related questions. For example, one study provided the standardized script that clinicians were asked to use when issuing a delayed prescription, which was 235 words in length and would likely require a few minutes to read to their patients.[30] Delayed antibiotic prescription strategies requiring recontact would also require increased time for clinicians and patients compared with immediate antibiotics or delayed antibiotic strategies in which the prescription was given at the time of the visit with instructions to delay or with postdating.[70] Delayed strategies requiring the patient to return for collection of the prescription would also require more patient time.[70]

For standardized decision rules, although there would likely be an initial time investment for clinicians in getting oriented to its use, how the time burden of its implementation would compare to that of the usual care process of deciding whether immediate antibiotics are needed would likely vary based on the complexity of the decision rule. For example, the sore throat decision rule utilized in the single relevant study we identified, was very simple, only including scoring of four objective indicators (e.g., cough, fever greater than 38 degrees Celsius, swollen submandibular glands, and exudate on throat or tonsils), with a requirement for antibiotic prescription in the presence of three or four indicators, and would not be expected to require much clinician time.[31]

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

None of the seven studies of point-of-care CRP testing explicitly measured adverse consequences of creating and implementing the intervention. Four trials described the amount of time the various interventions required of the participants.[67,81,103,105] All of the trials targeted clinicians and conducted CRP training requiring between 26.5 minutes and 1.5 hours of participant time. One trial used an intervention with an internet-based training module (mean time 26.5 minutes) and a structured group meeting organized by the individual practices (required time not reported).[67] In two trials, CRP training took 30 minutes.[103,105] In the fourth trial, clinicians participated in a 1.5-hour educational seminar that included a review of evidence-based recommendations for the evaluation and treatment of acute cough illness as well as

evidence regarding the use of CRP serum levels in diagnosing pneumonia or "other antibiotic-responsive illnesses".[81]

One trial found possible long-term benefit of training clinicians in the use of CRP testing.[104] In this followup study of a previously reported trial,[105] clinicians who received the CRP test training were slightly less likely to prescribe antibiotics for subsequent acute RTIs during a mean overall followup time of 3.67 years after the intervention (30.7% vs. 35.7%; p=0.36), although the difference was not statistically significant. Of particular interest in this study was the fact that clinicians only performed CRP testing in 3.7 percent (11/294) of subsequent episodes of RTI during the followup period.

Procalcitonin Point-of-Care Testing

The five trials and two reviews of procalcitonin did not specifically measure or report on increased time burden on clinicians, sustainability of intervention (e.g., adherence to algorithm), or measures of resource use associated with ordering and interpreting the test. The studies reported a range of 1 to 4 hours for test results being reported to the clinician, depending on where and how it was processed and reported. In all studies, clinicians communicated with patients via telephone to provide instructions on antibiotic use following interpretation of the test result. In some the patients had all been given a prescription and asked to not fill it until they heard from the clinician. Those who were deemed to not need an antibiotic were asked to return the prescription by mail. While these procedures may have been study related, they do raise questions about what process is used for handling prescribing decisions when the decision is delayed until after the patient is no longer in the clinic.

System-Level Interventions

While none of the system-level intervention studies explicitly addressed potential adverse effects of implementing the interventions or reported on the time burden associated with developing, deploying or using them, one study reported a decrease in ordering in rapid streptococcal tests associated with their system-level intervention.[59] Physicians in the intervention group (29.1%) were significantly less likely to order rapid strep tests than control group (41.5%) (RR 0.75; 95% CI, 0.58 to 0.97). There was no difference in the proportion of physicians in the intervention versus control groups ordering chest radiographs however (21.2% vs. 20.7% respectively; age-adjusted RR 0.98; 95% CI, 0.60 to 1.62).

Multifaceted Interventions

No study using multiple interventions explicitly measured adverse consequences of the time burden used to create and implement the intervention, although some discussed dropout rates and participation rates, which may be related. Seven studies described the amount of time required by participants to engage in the intervention, undergo training sessions, or participate in site visits or workshops.[4,34,60,82,120,132,139,151,152] Times ranged from 5-10 minutes for patient-focused interventions[60,120] and anywhere from 30 minutes to one day for provider-focused interventions including physician education,[151] academic profiling,[4,132] evidence based training,[82] and training to implement clinical tools.[139]

Point-of-Care Tests Combined with Other Strategies

The studies of multifaceted interventions including a testing component did not specifically measure or report on measures of resource use associated with ordering and interpreting tests.

The GRACE consortium-supported RCT of CRP plus provider-focused communication training (described in Key Question 1) found that the multifaceted group had the highest time burden.[67] Briefly, the GRACE consortium-supported RCT compared internet-based training in CRP use, enhanced provider communication skills, or both in patients with URTI and LRTIs seen between February and March of 2011 across 259 primary care practices in six European countries.[67] The communication training was accompanied by video demonstrations of consultation techniques and an interactive booklet to use during consultations. Completion of training was 87.6 percent for CRP training and 87.0 percent for communication training. Mean number of minutes spent on the training Web site was statistically significantly higher for the combination training group (39.8) and the communication training group (37.4) compared with the CRP training group (26.5; p=0.003).

Discussion

Key Findings and Strength of Evidence

The key findings of this review for comparisons of interventions to usual care and head-to-head comparisons of different interventions are separately described in the in summary of evidence tables 20 and 21 below. The factors used to determine the overall strength of evidence grades are summarized in Appendix J. We included 133 unique randomized controlled trials and observational studies, most of which were fair quality. The lack of evidence on both the most important benefits and harms prevented assessment of the net benefit of most intervention types. **Appropriate** prescribing was only evaluated in nine studies and **resistance** was only evaluated in one study. For appropriate prescribing, although we sought to assess whether the definition of appropriateness affects the apparent effectiveness of interventions, this was not possible due to the potential confounding influences of a wide variety of other factors. For all outcomes, although we sought to determine whether strategies differed based on various patient, clinical, and contextual factors, this was also not possible for the same reason.

Comparisons to Usual Care

Table 20 summarizes evidence across outcomes for each intervention compared with usual care. Four intervention types stand out as having the best evidence because they were the only ones that found benefit for resistance or appropriate prescribing: **(1) Watchful waiting** is the only intervention that has any evidence of reducing **resistance** to 4-6 antibiotics compared with immediate prescribing (28% vs 56%; $P<0.02$); however, it is low-strength (1 RCT, N=223) and limited to children with AOM. Various other types of delayed prescribing approaches also result in lower rates of antibiotic **use** compared with immediate prescribing (absolute difference, range, -63% to -76%; 6 RCTs; N=1664), without any worsening of complications or other clinical outcomes, but the comparison to immediate prescribing limits generalizability of the above findings; **(2) Electronic decision support** has moderate-strength evidence of reducing **inappropriate** prescribing in acute bronchitis and AOM (range, -13% to -24%; 2 RCTs, N=12195), low-strength evidence that overall prescribing is reduced when there is adequate use (>50%) of the system, and low-strength evidence of no worsening of healthcare utilization or complications; **(3) two combined clinic-based education interventions** that targeted patients, parents, and clinicians have low-strength evidence of reducing **inappropriate** prescribing in children with pharyngitis and in adults with sinusitis (-10% to -27%; 1 RCT, 1 observational, N=2193); and **(4) A multi-faceted intervention that combined a clinical algorithm, clinical tutor training , and a 3-part provider education** has low-strength evidence of improving **appropriate** prescribing in patients with acute RTI in Mexico (+21.5%; 1 observational; N=1495), but its net benefit is unknown because its effects on complications and other clinical outcomes were not reported. The next tier of best evidence is for interventions with the highest reductions in overall prescriptions with no important consequences. For this next tier, procalcitonin stands out with the strongest evidence of reducing overall antibiotic prescribing for adults (absolute difference range, -12% to -72%; moderate strength; 5 RCTs; N=2820), with no impact on mortality. In contrast, four interventions that have proved to lack benefit in reducing overall prescriptions include public campaigns targeting adults, a sore throat decision rule, and procalcitonin and rapid viral testing in children.

Table 20. Outcomes for each intervention compared with usual care in mixed populations (unless otherwise noted)

Intervention	Appropriate prescribing, resistance	Overall prescribing	Complications and other clinical outcomes	Knowledge, SDM, clinician skills, time burden
Education				
Clinic-based: Parents	No evidence	Effective for any acute RTI for age ≤ 14 y (L)	No worsening of return visits for index acute RTI (L)	Improved knowledge in short-term (L)
Clinic-based: Clinicians	No evidence	Small reductions for acute RTIs, upper RTI and AOM, but not acute sinusitis or pharyngitis (L)	Unknown; no evidence	No evidence
Clinic-based: Combined patient, parent, clinician	Improved prescribing in pharyngitis in children and sinusitis in adults (L); no evidence on resistance	Modest reduction for acute RTI (M)	No worsening of AOM complications or of patient or parent satisfaction for acute RTI (L)	No evidence
Community-based: Parents	No evidence	Moderately reduced for AOM (L)	No worsening of acute RTI complications (L)	Inconclusive evidence
Community-based: Adults	No evidence	Not effective (L)	Unknown; no evidence	Inconclusive evidence
Communication	No evidence	Moderate to large reduction for acute RTIs (M)	No worsening of acute RTI complications (L). Inconclusive for reconsultation, symptom improvement, patient satisfaction, or physical or mental quality of life	Inconclusive evidence
Clinical Interventions				
Delayed vs immediate prescribing	Watchful waiting reduced multi-drug resistance for S pneumonia strains in children with AOM (L); No evidence on appropriate use	Significantly reduced use (L)	No worsening of complications, adverse drug effects or reconsultations and *reduced* diarrhea in AOM; but reduced satisfaction and increased persistence of moderate to severe symptoms	No evidence
Sore throat decision rule vs. usual care	No evidence	No reduction (L)	No evidence	No evidence
CRP vs. usual care	No evidence	Moderate reduction (L)	Greater risk of reconsultation within 4 weeks (L), inconclusive for hospital admissions, symptom improvement and patient satisfaction	Inconclusive for patient knowledge; no evidence for time burden

Intervention	Appropriate prescribing, resistance	Overall prescribing	Complications and other clinical outcomes	Knowledge, SDM, clinician skills, time burden
Procalcitonin vs. usual care	No evidence	Large reduction in adult patients with upper RTI or acute bronchitis presenting to primary care or EDs, and those presenting to primary care with upper or lower RTI.	Adults: No worsening of mortality or treatment failure at 30 days in primary care or ED for acute bronchitis, upper RTI, or presenting to primary care with upper or lower acute RTI (L); no worsening in the # of days with limited activity or missing work or continuing symptoms at 28 days post-baseline for upper or lower RTI in primary care Children with suspected AOM: Use of an adult algorithm worsened AEs, but does not worsen composite outcome of AE/lack of efficacy or hospitalizations (L)	
Point-of-care viral testing	No evidence	Not effective in children (L), inconclusive in adults	No evidence	No evidence
Point-of-care streptococcal antigen testing (rapid strep testing)	Inconclusive for appropriate prescribing; no evidence on resistance	Significant reduction for pharyngitis (L)	No evidence	No evidence
System Level Interventions				
Electronic Decision Support	Improved appropriate prescribing in acute bronchitis and AOM (M). No evidence on resistance	Inconclusive due to mixed findings	No worsening of healthcare utilization or complications (L)	No evidence
Multifaceted Interventions				
Clinical algorithm + clinical tutor training + 3-part provider education	Increased appropriate prescribing (L); no evidence on resistance	No evidence	No evidence	No evidence
Provider education + audit and feedback	No evidence	Not effective in children (L)	Did not decrease patient satisfaction (L)	No evidence
Provider education + delayed prescribing + peer academic detailing	No evidence	Inconclusive	No evidence	No evidence

Intervention	Appropriate prescribing, resistance	Overall prescribing	Complications and other clinical outcomes	Knowledge, SDM, clinician skills, time burden
Provider and patient education + practice profiling + academic detailing	No evidence	Reduced in bronchitis (L)	Did not worsen 1-month clinic attendance (L)	No evidence
Provider and patient education + CRP testing	No evidence	Reduced, primarily due to CRP component (L)	No evidence	
Provider communication training + CRP testing	No evidence	Significant reduction (L)	Increased hospitalization; more days of moderately bad symptoms; but similar reconsultation, diagnostic testing use, and days off work (L)	Inconclusive

Head-to-Head Comparisons

No head-to-head trials have directly compared any of the top four interventions identified above that have the best advantages over usual care. Table 21 below summarizes the findings from studies that compared different interventions between different categories and within categories and those that evaluated augmentation of a primary intervention with a second intervention. Studies that compared different interventions within and between intervention categories found some differences; but some were of unclear importance. For sore throat, however, use of the FeverPain clinical score may be a better choice over delayed prescribing because it both reduced overall prescriptions and led to one fewer day of moderately bad or worse symptoms.

In the augmentation studies, more was not always better. The best evidence supports use of adding a clinical decision support system to a public education program because the combination improved **appropriate** prescribing (moderate strength), but we still have uncertainly about how it might affect other important outcomes. Multifaceted interventions that include certain POC tests may reduce overall prescribing more than their non-POC components alone, but not the POC components alone. Adding communication training to clinician education may not be worth the potential additional effort as the combination did not lead to improvements in appropriate or overall prescribing. Adding CRP testing to a clinical algorithm and adding patient education to delayed prescribing have unclear usefulness as available evidence was mostly inconclusive.

Table 21. Outcomes for head-to-head comparisons of interventions in mixed populations (unless otherwise noted)

Intervention	Appropriate prescribing, resistance	Overall prescribing	Complications and other clinical outcomes	Knowledge, SDM, clinician skills, time burden
Comparisons Between Intervention Categories				
Communication vs CRP	No evidence	Inconclusive	Borderline fewer reconsultations with CRP (L); similar effect on patients' symptoms (L)	No evidence

Intervention	Appropriate prescribing, resistance	Overall prescribing	Complications and other clinical outcomes	Knowledge, SDM, clinician skills, time burden
Comparisons Within intervention categories: Clinical				
Different delayed prescribing strategies	No evidence	No differences (L)	Similar complications, diarrhea or rash, duration of moderately bad symptoms, reconsultations, or satisfaction; but vomiting and abdominal pain highest with giving prescriptions with instructions to delay (L)	No evidence
Delayed prescribing vs. clinical score	No evidence	Greater reduction with FeverPAIN score use in sore throat (L)	Similar return visits, but delayed prescribing leads to an additional day of moderately bad or worse symptoms in patients with sore throat	No evidence
Augmentation				
CRP plus clinical algorithm vs. algorithm alone	No evidence	Inconclusive	Inconclusive	
Enhanced provider communication + CRP vs each alone	No evidence	Lower than communication training alone but not CRP alone, particularly those with LRTIs. (L)	Similar hospitalization, median number of days of moderately bad symptoms, reconsultation rates, diagnostic testing use and days off work (L)	Combination had highest time burden (L)
Combining rapid strep testing plus a decision rule vs. various comparators	No evidence	Lower than delayed prescribing, the decision rule alone, but not rapid strep testing alone in sore throat (L)	Similar symptom improvements and return visits (L)	No evidence
Adding a clinical decision support system to a public education campaign	Improved appropriate prescribing (M); no evidence on resistance	No evidence	No evidence	No evidence
Adding communication training to clinician education	No improvement in *appropriate* prescribing (L); no evidence on resistance	No improvement in *overall* prescribing (L)	Inconclusive	No evidence
Adding patient education materials (e.g., leaflets) to a delayed prescribing strategy	Inconclusive	No evidence	More clinic visits (L)	No evidence

Differences in Outcomes According to Potential Moderates of Effect

Intended Target of Intervention

The intended target of the interventions varied in the education interventions, where the reductions in prescribing were greater when the target was the patient or parent, and somewhat less when the target was the clinician or combined groups. However, direct comparisons were not available and the ranges in rates of reduction overlapped across the groups such that a clear pattern could not be established. It was clear that combining patient and clinician education did not result in clearly greater reductions. Clinical outcomes, including patient or parent satisfaction were not significantly affected. With interventions aimed at improving communication, only clinician-targeted interventions were found to have beneficial effects, although the patient-targeted evidence was very limited. Other interventions were either aimed only at clinicians (e.g., point-of-care tests), or always included both clinicians and patients (e.g., delayed prescribing).

Specific Acute Respiratory Tract Infections

The results for studies that either enrolled patients with specific acute RTIs, or reported results stratified by type of RTI, are presented in Table 22, below. Interventions with mixed results by RTI type were patient education (with evidence of effectiveness for pharyngitis but not for acute otitis media), clinician education (with evidence of effectiveness in acute otitis media and pharyngitis but not sinusitis), combined patient and clinician education (with evidence of effectiveness in bronchitis but mixed evidence for pharyngitis and sinusitis), and the addition of clinician communication training to guideline education (which was found effective for sinusitis but not for bronchitis). Three interventions were found to have a significant effect in improving antibiotic use across three RTI types; electronic decision support and two multifaceted interventions. Both involved clinician and patient education, but one added CRP testing and the other added academic detailing and practice profiling. We had no evidence on the effect of other patient characteristics on any outcome (i.e., signs and symptoms [nature and duration], when counting began for duration of symptoms, previous medical history [e.g., frailty, comorbidity], prior RTIs, and prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained).

Table 22. Effectiveness of interventions in improving antibiotic prescribing by respiratory tract infection type appropriate

Intervention Category	Acute Otitis Media	Bronchitis	Pharyngitis	Sinusitis
Patient and clinician education		+	Mixed	Mixed
Patient education	-		+	
Clinician education	+		+	-
Electronic decision support	+	+	+	
Delayed prescribing	+			
CRP testing				+
Procalcitonin testing		+		
Rapid strep testing			+	
Multifaceted interventions:				
(1) Physician education, (2) practice profiling, (3) academic detailing, and (4) patient education		+	+	+
(1) Provider education, (2) patient education, and (3) workshops on and access to rapid tests and CRP test		+	+	+
Adding clinician communication training to guideline education		-		+
Adding an educational leaflet for patients to a suggestion to delay prescription filling		+		

Seasonal Influences

Most of the studies were timed for the season with highest prevalence of disease, mainly winter months, and no clear pattern could be discerned in the results based on this factor. Local tailoring was typically done for educational interventions (e.g., using ethnically sensitive materials). Comparisons of no tailoring versus tailoring or between degrees or methods of tailoring were not possible due to the wide variation in the combinations of specific intervention details, population, and outcome measurement across studies.

Baseline Prescribing Rates

A key background factor may be baseline prescribing rates, which varied extremely widely across studies (from a low of <10% to greater than 90%) and situations where the background prescribing was declining during the study period. While this is likely true, the poor reporting of this information severely limits the ability to analyze the potential impacts. Other background contextual factors (i.e., known patterns of disease activity [e.g., an influenza epidemic, a pertussis outbreak], or system-level characteristics) were not studied explicitly and were reported inadequately to allow analysis.

We did not find evidence on other factors as potential effect modifiers (i.e., clinician characteristics such as specialty, number of years in practice, type of clinic organization, geographic region, and population served or diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty).

Findings in Relationship to What is Already Known

Several systematic reviews of interventions to improve appropriate prescribing have been conducted previously. While some primarily focused on a single intervention (e.g., delayed

prescribing or rapid strep tests)[14,164,168] and were included here where possible, few assessed a broad range of interventions and none included the range of outcomes addressed in this review. A Cochrane review from 2005[169] included any professional intervention, as defined by the Cochrane Effective Practice and Organisation of Care Group (EPOC), or a patient-based intervention. This review included 39 studies and concluded that the most effective intervention needed to be targeted to specific problematic prescribing behaviors, with no single intervention suitable for all. In contrast to our report, they concluded that multifaceted educational interventions were the only interventions with effect sizes of sufficient magnitude to potentially reduce the incidence of antibiotic resistant bacteria. Similarly, an AHRQ report on quality improvement strategies concluded that while no single strategy is clearly superior, clinician education and delayed prescribing may be more effective in certain settings and that interventions targeting prescribing for all acute RTIs may be more effective than those that target a single type of RTI.[3] These reviews come to differing conclusions compared with our report for multiple reasons, including the addition of a large volume of newer evidence, the use of a formal system to grade the strength of the evidence, and the scope of interventions considered (e.g., point-of-care tests).

There are several professional organizations and societies that have issued guidance for clinicians on diagnosing and treating conditions that fall under the acute RTI umbrella, with some making recommendations that overlap with this report. In some cases they recommend delayed prescribing of antibiotics (one recommends specifically to educate patients) but no other interventions reviewed here are recommended for or against. The American Academy of Pediatrics (AAP), for instance, recommends that for children age 2 to 12 years presenting with nonsevere symptoms, observation for up to 72 hours (i.e., delayed prescribing) is reasonable depending on the patient's age, diagnostic certainty and illness severity. The AAP also recommends that three days of observation is an alternative to immediate prescribing in children presenting with persistent sinusitis. However, the American Academy of Family Practice (AAFP) issued guidance on treating bacterial sinusitis in children or adults that uses strict criteria for identifying patients with bacterial sinusitis, and recommends against delayed prescribing in these patients. Both the Michigan Quality Improvement Consortium (MQIC) and the American College of Chest Physicians (ACCP) have issued guidance that recommends against prescribing antibiotics in patients with uncomplicated acute bronchitis and for educating patients and families. For pharyngitis, both the MQIC and the Infectious Disease Society of America (IDSA) recommend using the rapid strep test before deciding on antibiotic use.

Applicability

As planned in our protocol for this review, we focused our reporting on applicability of the body of evidence on the subgroups specified in Key Questions 1 through 4 (subquestions a through e) within the elements of the PICOTS framework.

Population Characteristics

Patients

The studies enrolled a variety of patient types, with 29 percent enrolling only adults while the remainder enrolled either children or any age group. While 61 percent of the studies included assessments of any acute RTI, the specific infections that were most commonly studied were pharyngitis (including 'sore throat' and tonsillitis) and acute otitis media. The least commonly

reported infection was rhinitis. Acute bronchitis, sinusitis, and cough or common cold was studied specifically in similar proportions of studies (20% to 30%). Reporting of other patient characteristics such as previous medical history, prior RTIs, prior use of antibiotics, educational level, ethnicity, and socioeconomic status were reported in less than 20 percent of studies, such that the applicability of the body of evidence was not clear.

Clinicians

Information on clinicians studied was reported sporadically and inconsistently. While studies of acute otitis media in children typically included pediatricians and family medicine physicians, the specialty of clinicians in other studies were variably reported and very rarely analyzed. Most studies (81%) were conducted in general practice or primary care, but few reported on clinician specialty (14%), the mean number of years of practice (13%), or population served (25%).

Intervention Characteristics

Education

Clinic-based interventions were generally locally created with similar messages but with a wide variation in the method, duration and intensity of application. Community-wide campaigns varied in terms of the number and types of specific interventions and how they were locally tailored. All the interventions could be used in routine care in the United States.

Communication

Communication training varied from in-person to online methods and varied in intensity and duration.

Delayed Prescribing

Methods varied widely from leaving the decision to the patient, requiring the patient to return to the clinic, or other methods. All methods were likely to be in use in routine care and analysis indicated little variation in findings by method of delaying prescribing.

Point-of-Care Testing

CRP and procalcitonin interventions followed algorithms for assisting in determining the need for antibiotics. The guidance varied somewhat across studies of CRP, which may have added to the heterogeneity seen in pooled analysis. Procalcitonin algorithms were consistent across studies. Rapid viral tests included one that was multiviral and the rest were specific for influenza. Diagnostic accuracy for rapid viral and strep tests was reported in some studies, but these were similar across studies as were the findings. The turnaround time for test results varied across these studies, with some reporting the time as minutes and others as hours.

System-Level Interventions

The interventions varied somewhat, with some using a computer decision support tool that required the clinician to access it actively, while others used a ‘pop-up’ screen based on electronic prescribing entry.

Multifaceted Interventions

This group of studies involved a very wide range of combinations of interventions, most often including some form of education and/or communication training combined with other interventions. We stratified by number and type of interventions, but the variability limited the ability to generalize findings.

Comparators

Comparators for the interventions in this review were often usual care with very few comparing competing strategies. While a small number compared reasonable competing interventions, most studies of delayed prescribing could be described as efficacy studies because they compared to either immediate prescribing or no prescribing, rather than "usual care", which would result in a mix of immediate, no, and possibly delayed prescribing. For this report, we did not report comparisons to no prescribing.

Outcomes

By far the most commonly reported outcome was overall prescribing of antibiotics, while the key outcomes of resistance and appropriate prescribing were reported seldom and with inconsistent definitions and methods. The outcome of overall prescribing assumed in most cases that prescriptions written or filled were used, while few studies reported on actual use (mainly the delayed prescribing studies). Numerous outcomes identified as important by key informants and TEP members (e.g., quality of life, utilization of vaccines, and use of nonantibiotic treatments) were either not reported at all or rarely reported such that conclusions cannot be drawn. For the most part, studies evaluated outcomes over relatively short periods of time; typically a few months in a single season when the prevalence of the infection was the highest. Community-based interventions, such as educational programs that take time and resources to establish, reported outcomes over a period of 2 to 5 years. This time period allowed for patterns of effect to be seen. These studies often reported a clear trend towards lower antibiotic use for acute RTI over time in the control groups of these studies, such that snapshots of a single season may not reflect either current effectiveness or sustainability of an intervention.

Timeframes and Settings

A major drawback of the body of evidence is that 55 percent of the studies were conducted in countries outside the US. This is an issue for two reasons; the baseline or background prescribing rate varies by country, sometimes widely, and the healthcare systems, cultural attitudes, and behaviors of clinicians and patients may vary enough in other countries to reduce the generalizability of the findings to a US population. While the relative change in an outcome may be similar across widely varying baseline rates, the ultimate outcome of reducing resistance while maintaining or improving clinical outcomes most likely requires a specific absolute reduction or a threshold of prescribing to be achieved. We found that for some interventions the relative and absolute effects were much larger when the baseline prescribing rate was very high, although this was not consistent across studies of all interventions. Related to the reasons for higher or lower baseline prescribing rates were the cultural aspects involved in prescribing for acute RTI and system-level differences in how care was provided. System-level interventions such as computer aided decision support systems are relevant to more economically developed

systems, while delayed prescribing interventions effectiveness may vary depending on the typical ease of access patients have to providers and pharmacies.

The timeframe for the studies varied by the number of years and seasons studied, as noted above in our discussion of outcomes. Additionally, the years of the study may also be relevant in the situation where the background rate of prescribing antibiotics for acute RTI is declining. Older studies may have less relevance because, for example, if the prescribing rate has already declined to a low level relative to other settings or timeframes, there may be little opportunity to show an effect of an intervention.

Implications for Clinical and Policy Decisionmaking

In an effort to improve appropriate prescribing of antibiotics for acute RTIs, clinicians and policymakers need to make choices among the relevant interventions based on the best evidence. With the ultimate goal being reduction in antibiotic resistance, the best evidence to date is for using a delayed prescribing or watchful waiting approach. Although delayed prescribing has mainly been compared to interventions that do not reflect usual care, it has been shown to result in less resistance to antibiotics, to be effective in reducing overall antibiotic use and is easily implementable. While it seems clear that patients will experience symptoms longer and will have lower satisfaction compared with receiving a prescription immediately, comparison to usual care where there would be a mix of immediate, delayed, or no prescribing may result in fewer differences.

The next tier of best evidence is interventions shown to improve appropriate prescribing. These include patient and combined patient and clinician education programs. Patient education can be simple, for example, waiting room posters featuring a letter from a local clinician. Clinician education programs should be locally tailored and the balance of program intensity and clinician participation needs to be taken into consideration. Electronic decision support systems have been show to improve prescribing for bronchitis and acute otitis media and may be easily implementable in electronic medical record systems. The resources required to initiate the program and for clinicians to use such systems has not been studied. Multifaceted interventions shown to improve appropriate prescribing are those that involve an electronic decision support system combined with community education for parents, and a program combining a clinical algorithm with clinician education. Unfortunately there is no good evidence on the relative sustainability of these interventions. Even the comparison across the interventions or the combining of them for synergy is less well studied than is needed.

While the evidence on rapid strep tests, procalcitonin and CRP was limited to overall antibiotic use and other secondary outcomes, these interventions appear to hold promise, as the reductions in overall prescribing can be larger than with other interventions. Evidence does not support the regular use of viral testing as a way to improve appropriate prescribing of antibiotics at this time. The reasons for this finding may be multifactorial and may include test accuracy limitations. For both CRP and procalcitonin, implementation is restricted somewhat by the limitations of the current algorithms used to guide clinicians. With CRP, there is a lack of standardization across the algorithms in terms of consistent guidance for clinicians on how to interpret and act on the test results such that it cannot be recommended for standard use at this time. For procalcitonin, while there is agreement across algorithms in terms of thresholds for antibiotic use, they were developed for use in adults and use in children led to increased antibiotic use. For all the of the point-of-care tests, additional work is need to evaluate the

tradeoffs in resource use required, specific populations where they are best used, and their sustainability as an intervention.

Limitations of the Review Process

Potential limitations in our process include the exclusion of non-English language publications. To explore the impact of this limitation we reviewed the English-language abstracts of studies with full text published in other languages for apparent eligibility. We identified 24 potentially relevant non-English language studies with English abstracts, of which only one was an RCT (of CRP testing) whose findings as reported in the abstract did not differ from the included studies. The remainders were mostly observational studies whose design and eligibility would require review of the full text, but none were evaluating interventions that we did not have evidence about from English-language publications. Therefore we do not believe that exclusion of non-English language studies has significantly affected the conclusions of this review. Please refer to Appendix C for citations of non-English language studies with English abstracts that were excluded from this review.

Another potential limitation involves our literature search strategies. We conducted extensive literature searches with carefully constructed electronic database strategies that underwent peer review and multiple iterations (Appendix A). However, we found that this topic area is difficult to search for as there are no standard search terms that cover the interventions and outcomes of interest. Thus, it is possible we were unable to identify all potentially relevant studies. In our early discussions with our TEP, we established 1990 as the earliest year that studies would be relevant, but agreed upon using good quality systematic reviews to identify studies published between 1990 and 2000 for efficiency. It is possible that in using this method we may have missed some older studies, if those reviews had not identified them. To overcome this possible limitation, we utilized our TEP members to assist in identifying missing studies by sharing our included study list with them early on, contacted manufacturers of point-of-care tests, and searched reference lists and bibliographies of included studies. Each of these methods was successful in identifying additional citations for consideration.

The final limitation to note is the exclusion of observational studies that did not either control for potential confounding, or were simple before-after studies without a time-series design. We established this criterion to focus our efforts on better evidence (i.e., evidence with lower risk of bias). However, in doing so, it is possible that an important study was missed. In an attempt to overcome this limitation, we allowed any form of controlling for confounding, including simple stratification of results by potential confounders.

Gaps in the Evidence Base

Several gaps and serious limitations of the evidence base limited our ability to reach strong conclusions with regard to several aspects of this review. We used the framework proposed by Robinson et al[170] to outline these limitations; classifying identified gaps as insufficient or imprecise information, biased information, inconsistency or unknown consistency, and not providing the right information. The gaps are also organized according to the PICOTS framework, by which issues relating to limitations of applicability are identified as well. These are summarized in Table 23 below. Issues pertaining to the overall body of evidence for this report include study design and conduct, the specific details of interventions, choice of comparators and more. In our sample, only 39 percent of the RCTs were cluster randomized. Since many of the interventions were applied at the level of the clinician or even the clinic,

allocating the intervention at the patient level was not ideal because of the risk for contamination of samples (i.e., patients and clinicians may talk to each other about the intervention and influence outcomes). Thus, the most appropriate design for most trials of these interventions is a cluster randomized trial. While we cannot know the direction of the bias introduced by potential contamination, it is likely that lack of clustering could reduce the observed impact of an intervention or differences between interventions.

In our review, we identified some indications for which specific interventions were beneficial or not beneficial for specific outcomes. The limitation here is that not all studies reported the outcomes stratified by such population groups, and some reported groupings of population groups that may have incorporated multiple specific indications, for example studies that stratified results by LRTI versus upper RTI.

We were limited in our ability to combine studies and to draw strong conclusions in part due to the variation in the specific details of interventions within a single category. For example, while we found multiple studies of enhancing clinician communication skills, the methods used varied enough that combining these studies led to significant statistical heterogeneity that was not resolved with subgrouping or sensitivity analyses. Other examples are in the group of studies on clinic-based methods to educate patients or parents. These interventions varied widely, with each study representing a 'one-off' intervention (e.g., videos featuring local pediatricians, videos with animation, posters of 'commitment letters'). While these may be viewed as being locally tailored, they varied enough that we could not combine them, and collectively they do not provide a cohesive picture of the benefits of educating patients using a core set of principles. Unfortunately, the variation in both categories and specific details of interventions used in multifaceted intervention studies seriously prevented drawing meaningful conclusions from an area of research that is likely to hold the key to identification of the most effective intervention.

Similarly, we found that the comparisons made by studies to date are too varied to be as useful as they could be in drawing meaningful conclusions. For example, delayed prescribing as an intervention was compared with always providing a prescription in some studies and with not providing a prescription in other studies. These comparisons are less generalizable to other study designs where the comparison is to usual care or to a competing intervention. In addition, the majority of studies do make comparisons to a usual care group, with fewer studies evaluating comparisons of competing interventions.

The specific outcomes reported and how they were measured also varied and created difficulties in combining similar studies and drawing strong conclusions. A simple example is the outcomes in Key Question 1 regarding the comparative effectiveness of interventions to improve appropriate antibiotic use in acute RTIs. Here the evidence gap is largely not having the right information. Only 5 percent of studies attempted to assess and report on the outcome of appropriate use. The remainder reported overall prescribing and sometimes use of antibiotics, with the assumption that any reduction reflects mostly reduction in uses that are outside the definition of appropriate. The studies that did report on appropriate prescribing and use varied widely in how they identified appropriateness. Very few met the standard of including a definition set *a priori* and using chart review to establish whether the cases met these criteria. In particular, some used only ICD-9 coding to identify appropriate uses. For the large number of studies reporting on overall antibiotic prescribing and use, the definitions and methods to measure the outcome again varied enough to limit the ability to pool many of the studies. Some measured prescriptions filled using pharmacy data, and others used surveys of patients and clinicians to report what was prescribed and used.

Related to either overall or appropriate prescribing outcomes, there is a gap in consistently defined goals for the necessary change or difference in prescribing that will result in meaningful benefits, such as reductions in antibiotic resistance in intervention communities. While most of the RCTs did conduct power calculations to determine adequate sample sizes, the delta used to determine these ranged widely, with no reasoning given for the selection of the difference. For example, it is not clear that a difference in antibiotic prescribing of 15 percent is enough to make differences in key outcomes such as resistance, patient outcomes, satisfaction, and resource use. Without such information, it is difficult to evaluate the magnitude of difference seen in studies even when statistically significant. Similar concerns can be raised about other outcomes. For example, symptom improvement was often measured using mean change, without any parameters for judging the importance of the change/difference (e.g., differences in change of temperature of less than one degree Fahrenheit).

For other Key Questions, while similar issues arise, the real gap is in outcome reporting in general. Few studies reported on clinical consequences of reduced prescribing, and those that did were inconsistent in definitions and methods. No study explicitly attempted to measure resource use. Given the clear differences in the potential for differential cost (both monetary and intangible costs) this is a major gap in understanding which intervention or combination of interventions is best in which situation.

We were limited in drawing conclusions about how the effects of the strategies may differ in specific subgroups based on previous medical history (e.g., frailty, comorbidity), prior use of antibiotics, ethnicity, socioeconomic status, clinician characteristics, and other subgroups because studies rarely conducted subgroup analyses on these factors and these factors were not commonly reported, limiting our ability to look across studies. Due to potentially confounding influences of a wide variety of sources of variability, it is difficult to establish a relationship between any one subgroup characteristic and outcome.

With regard to settings, there is a potentially major issue with attempting to use study results from studies in settings outside the US. There may be cultural differences that result in wide variation in baseline prescribing, the application and uptake of specific interventions, and system-level differences that make this evidence nongeneralizable to the US setting. Given that 55 percent of included studies were conducted outside the US, this is potentially a serious limitation.

Table 23. Evidence gaps for interventions to improve appropriate use of antibiotics in acute respiratory tract infections

Key Question/Outcome	Category	Evidence Gap
KQs 1 and 2: Antibiotic prescribing, use and resistance.	General	Evidence of the comparative effectiveness of competing interventions is limited; the majority of studies compare to usual care with a high degree of variability in baseline prescribing across studies. Very limited evidence on comparative resistance patterns was available.
	Population	Limited evidence on effects in specific acute RTIs, particularly rhinitis. Limited evidence in older patients.
	Interventions and Comparators	Evidence for most interventions was limited by variation in the specific details of interventions within a single category. Evidence on comparisons between relevant competing interventions was very limited.
	Outcomes	Few studies evaluated appropriateness of prescribing, and for those that did there was wide variability in methods. Evidence on overall prescribing is limited by wide variation in ascertainment methods. There is a gap in consistently defined goals for the necessary change or difference in prescribing that will result in meaningful benefits, such as reductions in antibiotic resistance in intervention communities.
	Timing and Setting	For delayed prescribing and communication interventions, there is a gap in US-based research. The bulk of the evidence comes from outside the US, where cultural and system-level differences may limit generalizability of findings.
	Sources of heterogeneity	There is insufficient data to assess whether specific patient or provider characteristics, diagnostic method, or background contextual factors influence the comparative effectiveness of interventions.
KQs 3 & 4: Clinical outcomes, medical complications, healthcare utilization, and patient satisfaction	General	Evidence on clinical outcomes is very limited for most interventions (with the exception of delayed prescribing).
	Outcomes	There are large gaps in the evidence on medical complications (e.g., which are measured, how they are measured), healthcare utilization (e.g., definitions and time frames for return clinic visits, and patient satisfaction (e.g., validated methods and timing of measurement) due to inconsistent measurement and reporting.
KQ 5: Improved knowledge, improved shared decisionmaking, and improved clinician skills	General	Evidence is needed on whether or not the attainment of the intended intermediate outcomes is associated with the ultimate outcomes of interest.
KQ 6: Adverse events of interventions to improve appropriate prescribing for acute RTI	General	Information on adverse consequences of implementing interventions was completely absent.

Future Research Needs

Based on the gaps and weaknesses identified through the systematic review of the literature, the following areas present an opportunity for new research to support healthcare decisions. Studies of interventions to improve appropriate antibiotic prescribing in acute RTIs should have the following methodological features:

- Most studies in this area can be randomized and in such cases cluster randomization should be used.
- Nonrandomized studies must adhere to the best methods, particularly using methods to control for potential confounding.

- Interventions and comparators should be competing interventions from the best identified in this report.
- Interventions that involve changing behavior (e.g., educational and communication interventions) should be created based on the best evidence to date rather than designing a new intervention each time.
- Define appropriate prescribing and use. The definition needs to be clinically defensible, the ascertainment of this outcome needs to include some level of chart review, and the measurement of actual use needs to be considered.
- Measure resistance as an outcome.
- Measure clinical outcomes and adverse consequences of the competing interventions.
- Background contextual factors must be reported and considered, particularly baseline prescribing rates for particular acute RTIs.
- Patient and provider characteristics should be analyzed as effect modifiers.

Conclusions

The lack of evidence on both the most important benefits and harms prevented assessment of the net benefit of most intervention approaches because adequate evidence on was not available. Despite the enormous research efforts over the past two decades (129 studies in 137 publications, including 91 RCTs), the evidence is still largely inadequate to identify optimum intervention strategies for improving appropriate antibiotic use for acute RTIs. This is because most studies focused on overall antibiotic use and other intermediate clinical outcomes and not the most important outcomes of appropriate prescription and use of antibiotics and antibiotic resistance. The best evidence available supports the use of electronic decision support systems and educational strategies because they have the strongest evidence (moderate strength) of an improvement in appropriate prescribing. We have at least low-strength evidence that electronic decision support systems do not increase complication rates and educational interventions do not lead to a worsening of clinical outcomes. One point-of-care diagnostic test, procalcitonin, has the best evidence for reducing overall prescribing and no impact on mortality in adults (moderate strength). In contrast, neither procalcitonin nor rapid viral testing in children improved overall antibiotic use. While delayed prescribing results in lower rates of antibiotic use, the comparison to immediate prescribing limits generalizability. Future studies need to have rigorous design, assess appropriate prescribing and resistance to antibiotics, and evaluate the impact of important potential effect modifiers, such as background prescribing rates and clinician or patient characteristics.

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Abbreviations

Abbreviation	Definition
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACCP	American College of Clinical Pharmacy
AHRQ	Agency for Healthcare Research & Quality
CAP	Community acquired pneumonia
CER	Comparative Effectiveness Review
CI	Confidence interval
CRP	C-reactive protein
EHC	Effective Health Care
EPC	Evidence-based Practice Center
GRACE	Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe
ICD	International Classification of Diseases
IMPAC^{3}T	Improving Management of Patients with Acute Cough by C-reactive Protein Point of Care Testing and Communication Training
LRTI	Lower respiratory tract infection
NA	Not applicable
NS	Not significant
NSD	No significant difference
OR	Odds ratio
PCR	Polymerase chain reaction
PCR	Polymerase chain reaction
RCT	Randomized controlled trial
RR	Relative risk
RTI	Respiratory tract infection
TEP	Technical Expert Panel
URTI	Upper respiratory tract infection
WBC	White blood cell
WHO	World Health Organization